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THE PRINCIPLES AND PRACTICE

OF

ENDOCRINE MEDICINE

BY

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PREFACE.

The title of this book is meant to be accurately descriptive. The Practice of endocrine medicine is becoming daily a more important and fruitful field of medical labor; that such practice may be intelligent and scientific, an acquaintance with the Principles of the subject is indispensable. A sincere effort has been made to simplify these principles. In respect of points in doubt a short summary of arguments *pro* and *con* is given; but as far as possible controversial matter is abridged or omitted, and unsubstantiated claims are mentioned with proper reserve.

The book is primarily meant for doctors in active practice. The standpoint of the writer is that of the clinical practitioner—the physician in the presence of a patient with endocrine disorder. Symptoms and Diagnosis are discussed at length, and Treatment is emphasized. Many details of treatment and dosage are given which have been heretofore inaccessible in print in any language.

It is hoped that for general readers also the book may serve a useful purpose. It defines the actual scientific status of Endocrinology to-day, and contradicts at least a few of the old wives' fables now told not only in popular but in pseudoscientific literature as well.

In view of the practical aim of the book, many topics of exclusively scientific interest have been only touched on. But in each case, for the benefit of scientists and laboratory men, the important references to modern sources of information have been fully given, so that further special inquiry may be facilitated.

The laboratory and clinical experience of one student can no longer compass this large and growing field. I must make due and grateful mention of the valuable aid derived from previous scientific publications. Many of the papers in Barker's *System of Endocrinology and Metabolism* are excellent. Swale Vincent's *Internal Secretions and Ductless Glands* is particularly full for the Adrenal Gland, on which Dr. Vincent is an acknowledged authority. The enclyclopedic information in the slowly appearing successive editions and supplements of A. Biedl's *Innere Sekretion* has been

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freely used. For the Sex Glands F. H. A. Marshall's *Physiology of Reproduction,* and A. Lipschütz's *Internal Secretions of the Sex Glands,* are not only exhaustive, but fascinating as well.

To the editors and proprietors of *The New York Medical Journal and Record,* and of *American Medicine,* my sincere thanks are to be extended for permission to use again in modified form portions of articles I have recently contributed to their columns. These passages are indicated in the text as they occur. *The Journal of the American Medical Association* permits me to use several paragraphs from Marine and Kimball's article on the "Prevention of Goitre." Messrs. D. Appleton & Company have permitted the use of a page from one of my contributions ("Pituitary Gland") to The Blumer-Forchheimer System of Therapeusis. Messrs. Eli Lilly and Company have allowed me to reprint their Directions for the Use of Insulin (Iletin, Lilly), as approved by The Toronto Committee. It is also my pleasant duty to express the obligations I feel toward those from whom illustrations have been borrowed. The legend under each of them indicates its source.

Finally I must acknowledge with much gratitude the patience and courtesy of my publishers, Messrs. Lea & Febiger. Without their encouragement and support I should hardly have had the courage to complete so laborious an undertaking as the present one has proved to be. W. N. B.

NEW YORK, 1926.

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ENDOCRINE MEDICINE.

CHAPTER I.

INTRODUCTION.[1]

GLANDS IN GENERAL. CLASSIFICATION. DEFINITION AND DESCRIPTION. METHODS OF RESEARCH.

THE term gland is derived from the Latin *glans, glandis,* an acorn. The transfer of sense is rather fanciful. A gland may be defined as an *organ which secretes* (Latin inseparable prefix *se* apart, and *cernere,* sift or separate) *a substance, or substances subserving the chemical or physiological ends of the organism.*

The substance secreted may be of direct value to the organism (saliva, gastric juice), or may be an end-product, or toxin, or drug, or salt, requiring elimination, as happens in the urine. In the latter case the gland (kidney) is usually called *excretory* instead of secretory, but this distinction cannot be rigidly drawn; some glands (sweat glands, liver) perform both functions. Generally speaking, a secretory gland transforms chemically the material received from the blood; an excretory gland is a mere strainer.

GLANDS OF EXTERNAL SECRETION.

Some glands open externally on the skin or the mucous membranes. These are *glands of external secretion.* Structurally, in its simplest form, such a gland is a pocket, or pouch, or tubule (Fig. 1) connected with the skin or *primæ viæ* by a duct. The duct and gland proper are lined with a continuous layer of epithelial cells. The cells enclose a hollow called the *lumen,* into which the secretion is discharged, and in which it may be stored until needed. Secreting cells show often a peculiar granulation (Fig. 2) which is believed to be characteristic. The gland wall is made of connective tissue, with a complement of arteries, veins, lymphatics and nerve endings. External glands are of varying shape, size and structure. Some are simple or convoluted tubes (sweat glands, Fig. 3), some slightly branched, some extremely racemose (pancreas) and some of a non-typical structure (kidney, liver).

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[1] To facilitate reference to certain specially useful volumes, and at the same time conserve space, A. Biedl's Innere Sekretion (3d ed., and forthcoming 4th ed., Wien, Urban and Schwarzenburg, 1916 to 1924) is referred to all through this book as "Biedl," and the index of the volume in hand should be used to locate the quotation. Barker's System of Endocrinology and Metabolism (New York Appleton, 1922) is referred to as "Barker's System." Swale Vincent's Internal Secretions and Ductless Glands (3d ed., London, Arnold, 1924) is referred to as "S. Vincent." Only the first edition of Vincent's book contains an adequate bibliography. Barker's System and Vincent's volume are well indexed.

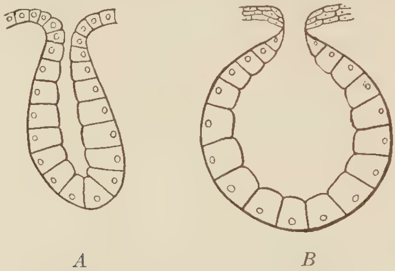

Fig. 1.—*A*, tubular gland from tongue of frog; *B*, acinous gland from skin of frog. (Smallwood.)

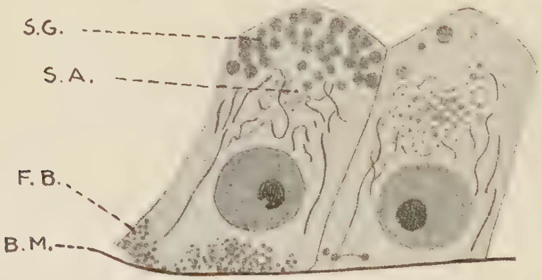

Fig. 2.—Two cells from the pancreas of the frog. The one on the left shows numerous secretion granules, *S.G.*, which are believed to contain the enzymes of the pancreas. Additional granules are in process of formation in the area indicated by *S.A.*, the secretion area. The cell on the right has discharged its secretion granules. *F.B.*, fat bodies of uncertain function. *B.M.*, basement membrane. There are other structures believed to be associated with secretion and the whole problem is far from settled. (Saguchi.)

Throughout the animal kingdom glands of external secretion subserve innumerable purposes. The most familiar secretions are those of the digestive system—saliva, gastric juice, bile, pancreatic fluid, succus entericus. Mucous glands moisten and lubricate mucous surfaces. Sebaceous glands (Fig. 4) soften the skin and oil the hair. Sweat glands excrete poisons and waste-products, and are besides intimately related to the maintenance of normal body temperature. Tear glands keep the cornea wet. Milk nourishes the offspring. Among certain lower mammals the odor of various gland secretions may be protective (skunk), or sex-excitative (bitch). Still lower are to be found the poison glands of snakes (defensive), the stinging glands of insects (Fig. 5) and

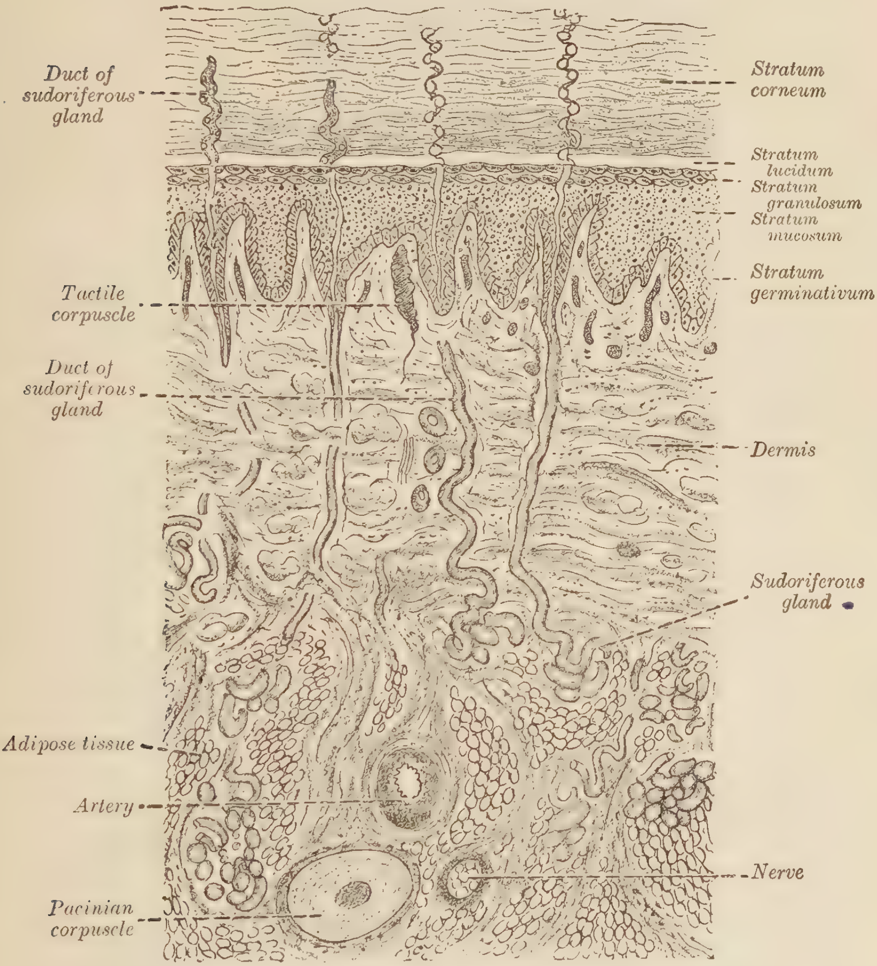

FIG. 3.—A diagrammatic sectional view of the skin (magnified), showing coiled sweat glands. (Gray.)

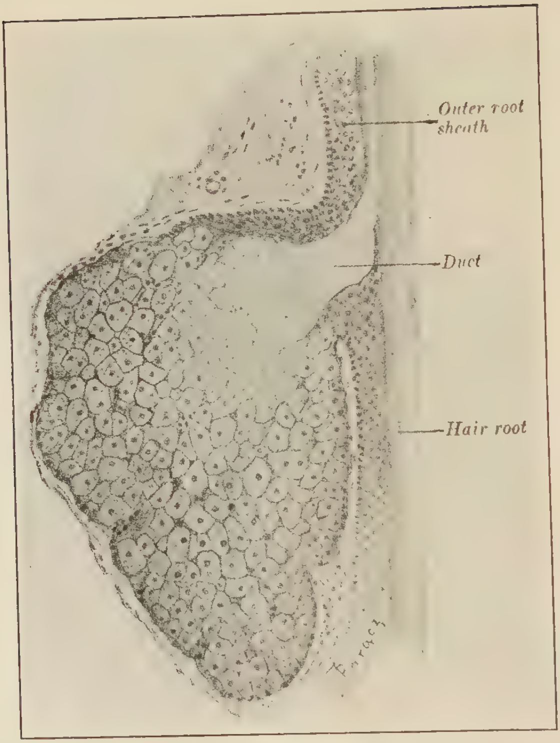

Fig. 4.—Sebaceous gland from human scalp. × 120. (Szymonowicz.)

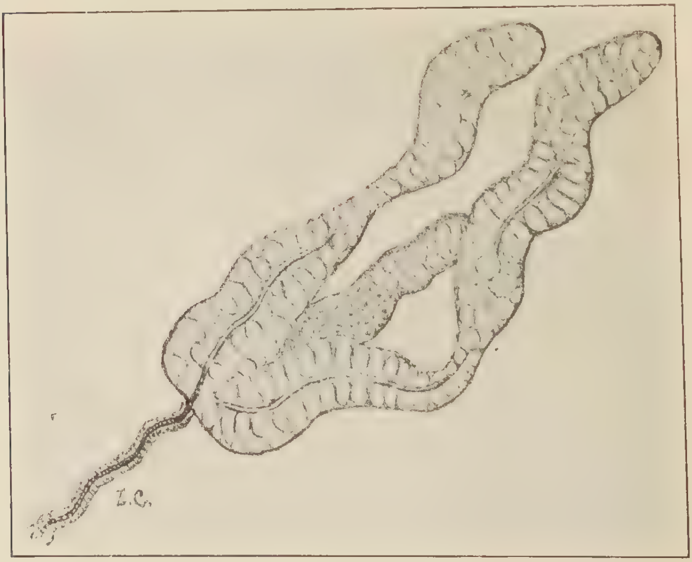

Fig. 5.—Salivary gland and duct of mosquito (Culex). Actual length of longer lobules less than 1 mm.

arachnids, the electric discharges from the skin glands of certain fishes like Malapterurus,[1] and quite a multitude of other curious secretions. Enough have been mentioned for purposes of illustration. Some limitation must be made in respect of the external secretion of the testis. This consists not only of fluid, but of flagellate cells (spermatozoa) which are not strictly chemical substances but organized bodies. Ovulation by the ovary is still harder to classify. A sebaceous gland also secretes cells, but they are broken down into oily granules, and the nuclei shrink and disappear.

GLANDS OF INTERNAL SECRETION.

Definitions.—Besides glands with ducts there are glands which have no ducts, but discharge their secretion into the veins and lymphatics with which they are abundantly supplied. These glands are called "blood glands," *glands of internal secretion, ductless glands,* or *endocrine glands.* The word endocrine is a recent artificial Greek derivative, *ἔνδον,* within, and *κρίνειν,* which means exactly the same as the Latin *cernere.* Endocrine has the merit of a handy adjective flexion. *Endocrinology is the systemized knowledge of the glands of internal secretion.*

Some other technical words must be noticed. There is some Continental use of the word *incretion* as a short substitute for internal secretion. *Incretion* and *incretory* have not so far been used to any extent in the United States. The word *hormone* was proposed by Bayliss and Starling, at the suggestion of W. B. Hardy, early in this century,[2] to include any substance secreted by one organ and carried thence through the circulation as a "chemical messenger" to excite action elsewhere, independently of the nervous supply. Secretin (see Chapter XII) was considered the type of such substances, and the word was apparently meant to include all the other internal secretions as well. When the word was found wide enough to include carbon dioxide, because this substance excites the respiratory center, Gley[3] suggested that carbon dioxide and other general metabolic products should be called *parahormones.* Schaefer[4] suggested that *autacoid* should be the general term for internal secretions, and that *exciting autacoids* should be called

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[1] Bayliss: Principles of General Physiology, 4th ed., London, Longmans, 1924, p. 660.

[2] Bayliss: Loc. cit., p. 712.

[3] Quoted by Bayliss: Loc. cit.

[4] Proc. 17th Internat. Cong. Med., London, Sect. II, Physiol., 1913, p. 21.

hormones, and *depressing* autacoids *chalones* (χαλᾶν, make slack, relax). The distinction seems somewhat artificial, and these terms have not been popular. But *hormone* is in general favor, and *hormonic* is a convenient adjective.

Claude Bernard[1] recognized clearly the existence of ductless glands. The phrase "internal secretion" seems to have originated with him, though Gley[2] thinks it was in use about the same time by other writers. Speaking of external glands, Bernard says: "Tous ces organes versaient au dehors du sang le produit de leur sécrétion. Mais il est un autre catégorie d'organes qui se rapprochent des organes glandulaires, avec cette différence qu'étant dépourvus de conduit excréteur, ils doivent déverser le produit de leur sécrétion dans le sang lui-même. C'est ce que nous avons désigné sous le nom de *sécrétions internes*, pour les distinguer des *sécrétions externes*, dont les produits sont versés au dehors du sang." He mentions as internal glands the spleen, lymph nodes, thyroid, adrenals, and calls the liver a gland with both functions (glucose, bile). He seems to have considered the serous fluids of the pleura and peritoneum, the cerebrospinal fluid, aqueous humor and synovia, also, as internal secretions.

In this connection it is well to explain that *opotherapy* and *organotherapy*—popular words in the circulars of the pharmaceutical manufacturers—mean treatment with organs or extracts of organs (ὄργανον, organ, and ὀπός, juice). This may or may not be the same as endocrine therapy. The use of extracts of kidney, or spleen, or lymph node, or prostate, is entirely unscientific; for we do not even know whether these organs have an internal secretion, nor, if they have, whether the preparation has been made in a proper way, and is absorbable without change from the alimentary canal.

Structure.—Endocrine glands, as such, have no ducts. Typically they consist only of trabeculæ or masses of cells, believed generally to be of epithelial origin—though this is not proved for the adrenal cortex or the gonads—supported by connective tissue and sometimes fat, and contained in a fibrous capsule. The thyroid gland (Fig. 15) is an exception. Here the cells line the walls of globular pockets or alveoli, which contain "colloid" (see Chapter IV), and the structure is plainly reminiscent of that of the external glands. Parathyroid glands in man occasionally show a few pockets. The *pars tuberalis* of the pituitary is pocketed (Fig. 33). Usually pocketing is entirely absent.

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[1] Leçons sur les liquides de l'organisme, 1859, **2**, 411, 412.

[2] Practitioner, 1915, **94**, 2.

Location.—The location of the glands of internal secretion is strangely haphazard, and can hardly be explained in some cases even by a careful review of the biological evolution. Among the mammalia the parathyroids may be outside of, or on, or in the thyroids of the same species. In man the adrenal cortex is tightly adherent to the adrenal medulla, though they have markedly different functions. The pituitary gland has for its curious resting place a little hollow in the base of the skull. The islands of Langerhans are buried in the pancreas. The testes are external to the abdominal cavity in some mammals, internal in others, and in some others again they descend only during the period of œstrus. It seems likely that man's post-simian assumption of the erect posture, while it has raised his brain heavenward, and gotten his eyes and nose out of the dust, has not promoted the welfare of all his internal secretions. The pressure (sometimes destructive) of hernia and varicocele upon the testes is greatly increased in the biped posture, and return circulation in the pancreas, liver, adrenals and gonads is entirely uphill.

Importance.—For the chemical welfare of the organism the internal secretions are of the first importance. A cat deprived of both its adrenals dies in a day or so. A child without a thyroid becomes a cretin. The precise functions subserved, however, are far more difficult and obscure than in the case of the external glands.

These questions will be severally dealt with as they arise. Here only a few incidental points will be noticed in order to clear up our point of view. The liver, for example, offers a difficulty in the matter of glycogen. Glycogen is made in the liver from portal glucose, stored there, and again released into the circulation as glucose when the needs of the system demand it. But we do not call glucose an endocrine secretion. The liver also has the peculiar property of converting toxic ammonia metabolites into the harmless urea. Biedl has proposed to call this a *negative internal secretion.* This property is, however, not usually included in the study of endocrinology.

Internal Secretions in Plants.—In respect of this topic, Bayliss[1] remarks: "Although there is no such effective way of chemical interchange in plants as there is in the circulating blood of animals, there is distinct evidence that chemical products of one part are able to influence the activities of other parts." Interested students are referred to the original passage, which contains references to the important recent literature.

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[1] Loc. cit., p. 729 b (p. 21 of this book).

Methods of Research.—1. *Anatomy and Pathology of the Glands.*—From the gross and minute structure of a ductless gland some general facts may be learned. Its absence may be significant; it may be definitely inflamed, or sclerotic, or atrophic. It may be cystic, or invaded by a tumor, or softened by reason of a failing blood supply. In some cases the changes are chemical or circulatory only, and especially in the parathyroids and the islets of Langerhans, there is often but little to be learned from the microscope. On the other hand, with the knife, or a stained section, thyroid troubles may often nowadays be quite readily identified.

2. *Excision of Glands.*—This method of research is of the greatest value. Most of all we know about the parathyroids, the adrenals, the internal secretion of the pancreas, has been learned in this way.

3. *Chemical Analysis.*—Modern methods in biological chemistry applied to the study of gland tissues have produced many brilliant results, and that study has just begun.

4. *Administration of Gland Preparations to Normal and Operatively Modified Animals.*—This furnishes an indispensable link in the chain of scientific evidence, but it must be remembered that all such results may be *pharmacological* only, not such as may be expected necessarily to occur in the normal organism.

5. *Clinical Study of Patients with Glandular Disease, and of Their Reactions to Endocrine Medication.*—To this topic much of the following volume is devoted.

CHAPTER II.

THE AUTONOMIC NERVOUS SYSTEM.

The autonomic nervous system is related in many important ways to the physiological action of the endocrines. A brief review of the subject is almost necessary to the proper understanding of some of the problems of endocrinology, particularly inasmuch as the newer studies, though still incomplete, have quite overset the former views of "sympathetic" nervous action.

One cannot make a better beginning than quote from W. Langdon Brown[1] the tribute of that author to Gaskell and Langley: "To read an account of the sympathetic nervous system before Gaskell is like reading a description of the circulation before Harvey. Just as even the course of the blood was in doubt before Harvey elucidated it, so even the direction of the impulses in the sympathetic chain was in doubt until Gaskell made it clear. But in both of these great works there are essential gaps. Harvey did not know of the existence of the capillaries, and Gaskell left many points in doubt as to the course and distribution of the sympathetic impulses. Our gratitude to Gaskell must not blind us to our debt to Langley, whose beautiful and accurate researches on the subject are of paramount importance. The elucidation of the plan of the sympathetic nervous system is almost entirely due to these two men, and remains one of the greatest achievements of the Cambridge School of Physiology."

Gaskell summarized much of his life work in the volume almost finished at the time of his death in 1915.[2]

The term "autonomic" was suggested to Dr. Langley by Prof. R. C. Jebb, in 1898, and as a comprehensive word for the entire involuntary system has been generally accepted. The words "involuntary" and "vegetative" are little used as synonyms.

Classification.—The autonomic nervous system is subdivided by Langley into (1) a *sympathetic*, (2) a *parasympathetic* and (3) an *enteric part.* The parasympathetic nervous system includes the cranial and sacral outflows; the sympathetic includes the thoracicolumbar outflow. Of the enteric system, Langley[1] remarks: "I pointed out (1900) that we should expect the cells of Auerbach's and Meissner's plexuses to be on the course of the bulbar and sacral nerves, but as there was no clear proof of their central connection, and as their obvious histological characters differed from those of any other peripheral nerve cells, I placed them in a class by themselves as the enteric nervous system. This classification is, I think, still advisable, for the central connection of the enteric nerve cells is still uncertain, and evidence has been obtained that they have automatic and reflex functions which other peripheral nerve cells do not possess."

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[1] The Sympathetic Nervous System in Disease, 2d ed., London, H. Frowde, 1923.

[2] The Involuntary Nervous System, London, Longmans, 1920; extensive bibliography.

This classification is evidently provisional. Various others are even more so. For details, the new text-books on physiology may be consulted.

In order to clear away some possible misapprehensions, a note by Bayliss[2] may be repeated here: "The whole autonomic system is in no sense an independent central nervous system, but an outflow from the cerebrospinal nervous system, distinguished by its connection with neurones lying entirely outside the latter, together with its formation of peripheral plexuses at the places of its distribution . . . It is entirely efferent. Sensory fibers found in some of its nerve trunks, such as the splanchnics, are ordinary afferent fibers having their trophic centers in the dorsal root ganglia, and merely taking their course in the sympathetic nerves, as sympathetic fibers are distributed in the nerve trunks of the voluntary system."

Physiology.—Some *definitions* may be helpfully reviewed. A *neurone* (or neuron) is the unit of nervous structure. It consists of a nucleated cell body with branched processes called *dendrons* or *dendrites* and one or two, or even three "axis-cylinder processes" (as formerly called) or *axones*. The axone (or axon) is of variable length and direction and at its termination ramifies over the cell body of the next neurone, or interlaces with the arborescent dendrites of the latter, thus making a *synapsis*, or *synapse*. The precise mode of connection is disputed; the fact seems established.[3]

In the *voluntary system* the typical *reflex arc* is subserved by three neurones (Plate I). The first, or *sensory* neurone, with cell body in the posterior root ganglion of the spinal nerve, makes a

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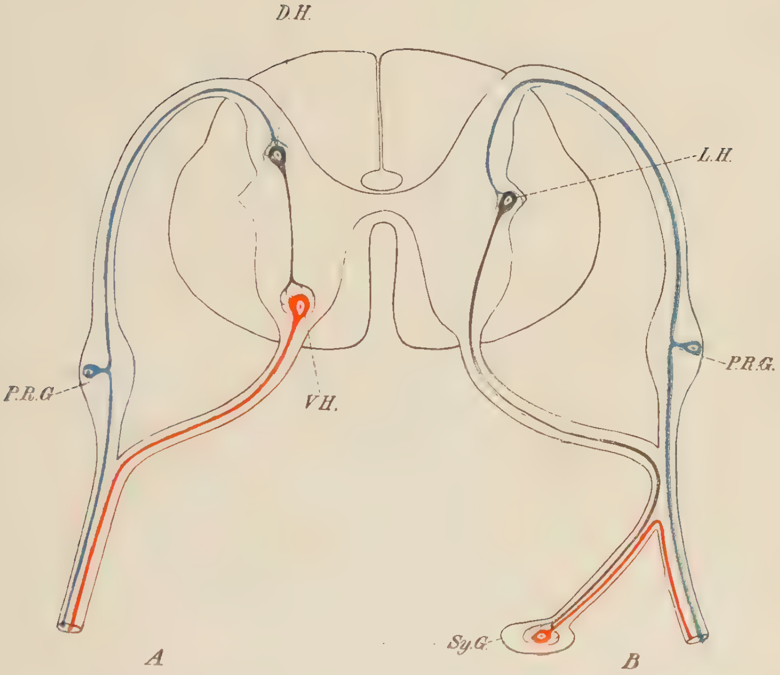
[1] Autonomic Nervous System, Cambridge, Heffer, 1921, Pt. I; references.
[2] Loc. cit., p. 21.
[3] Quain: Anatomy, London, Longmans, 1908.

PLATE I



Reflex paths in the cord. (From Gaskell)

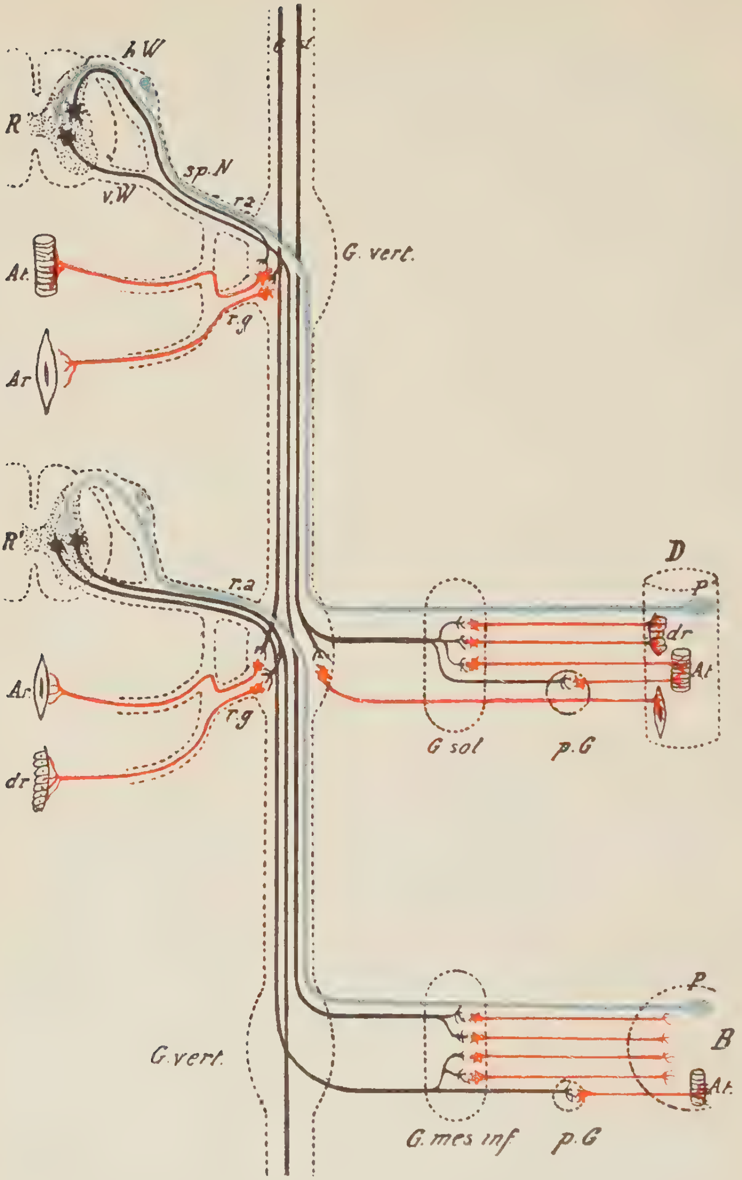
A. Of the voluntary system

The receptor neurons run in the posterior root, their cells lying in the posterior root ganglion, *P.R.G.* The connector neurons lie in the dorsal horn, *D.H.*, and connect with the excitor neurons lying in the ventral horn, *V.H.*, whose processes run in the anterior root.

B. Of the involuntary system

The receptor neurons run in the posterior root, their cells lying in the posterior root ganglion, *P.R.G.* The connector neurons lie in the lateral horn, *L.H.*, their processes running out in the anterior root and connecting, as the white ramus communicans, with the excitor neurons lying in the sympathetic ganglia, *Sy. G.* The processes of the excitor neurons form the gray ramus communicans and run out in the spinal nerve. (Both rami also carry—see Plate III—autonomic afferent neurons.)

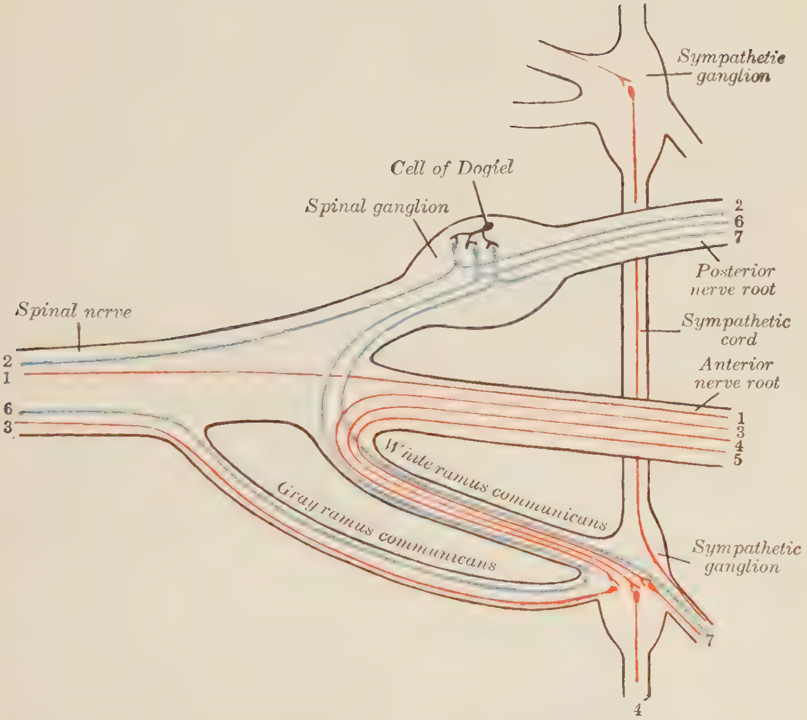
PLATE II



Scheme of nervous elements making up the sympathetic or splanchnic system. (By permission of Prof. Silvestro Baglioni)

R.R., spinal cord; *h.W.*, dorsal root; *v.W.*, ventral root; *sp. N.*, spinal nerve; *r.a.*, white ramus communicans; *r.g.*, gray ramus communicans; *G. st.*, lateral chain; *G. vert.*, ganglia of lateral chain (vertebral ganglia); *G. sol.*, solar ganglion; *p.G.*, peripheral ganglia (terminal); *G. mes. inf.*, inferior mesenteric ganglion; *D*, intestine; *B*, bladder. The left side of the figure shows the peripheral cutaneous system (*At.*, arterial walls; *Ar.*, erector muscles of hairs; *dr.*, gland cells). The right gives the peripheral splanchnic system (*At.*, arterial walls; *dr.*, gland cells; *P*, Pacinian corpuscles). The afferent paths and cells are blue; the efferent pre-ganglionic, black; the efferent post-ganglionic paths and cells, red.

PLATE III



Scheme showing structure of a typical spinal nerve. (Gray)

1. Somatic efferent. 2. Somatic afferent. 3, 4, 5. Sympathetic efferent.
6, 7. Sympathetic afferent.

PLATE IV

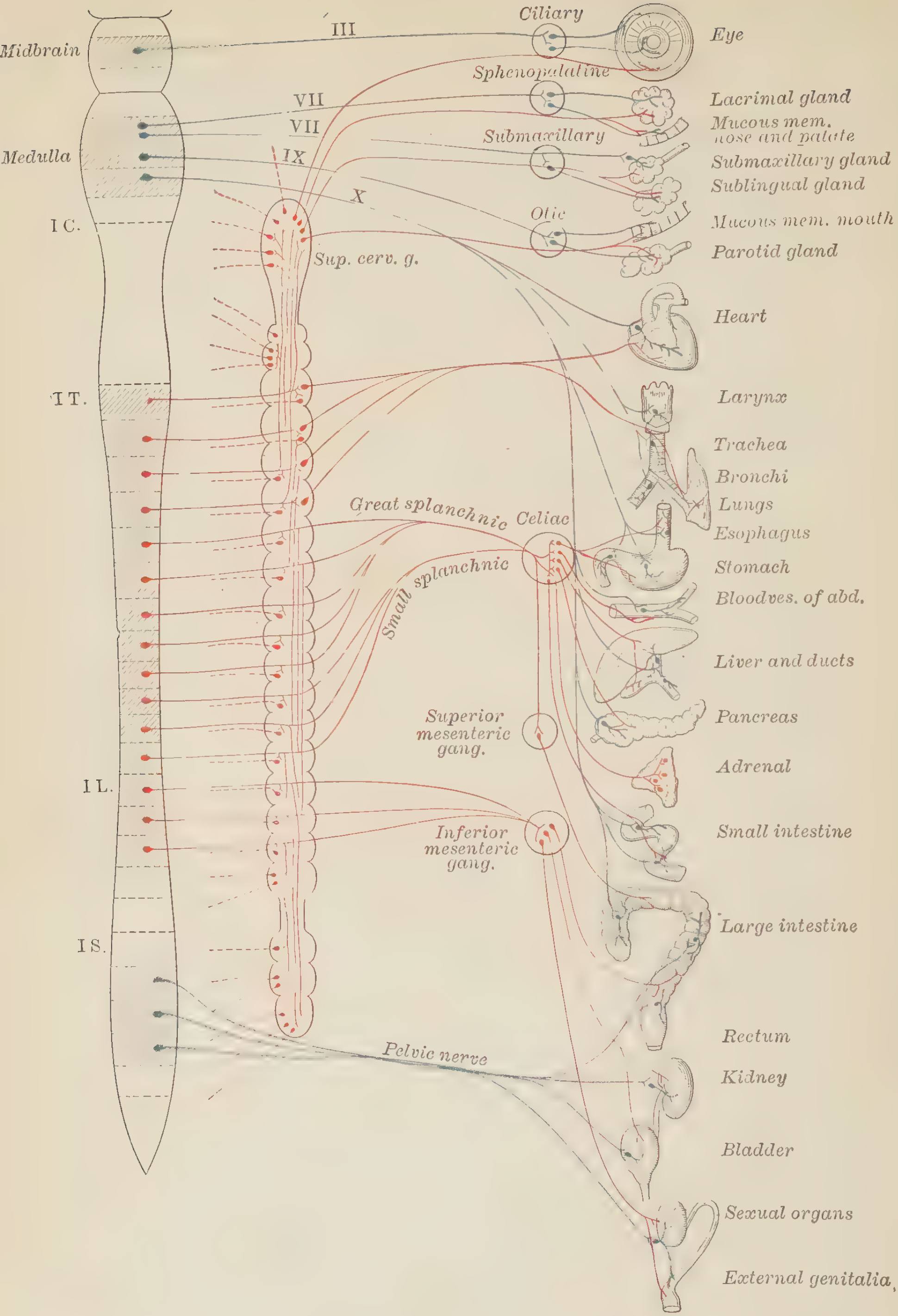


Diagram of efferent autonomic nervous system. (Modified after Meyer and Gottlieb)

Blue, cranial and sacral outflow. Red, thoraco-humeral outflow. ------, Postganglionic fibers to spinal and cranial nerves to supply vasomotors to head, trunk and limbs, motor fibers to smooth muscles of skin and fibers to sweat glands.

synapse with a gray cell in the posterior horn of the gray matter of the cord. This gray cell sends an axone to the anterior horn, with another synapse around a polypolar gray cell there. This third cell when stimulated originates the motor impulse, which travels by an axone escaping from the cord by an anterior root and goes to a voluntary muscle. The sensory neurone is also called *afferent* or *receptor.* The second neurone, which in this case is entirely in the cord, is strictly neither sensory or motor, and is called a *connector* or *preganglionic* (Langley) neurone. The third is *motor, efferent,* or *excitor* (*postganglionic* of Langley).

Now in the *autonomic system* the simplest reflex arc is somewhat different. A sensory message is conveyed as before to the ganglion cell on the posterior root, and thence not to the posterior horn cells, but to the lateral horn, where there is also a collection of nerve cells. With one of these a synapse is made. The cell of the lateral column sends an axone out at the anterior root.

This autonomic axone passes (in the dorso-lumbar region) by a *white ramus communicans* to the adjacent sympathetic ganglion of the dorso-lumbar chain, makes a synapse there (sometimes), and the third or excitor neurone returns by a *gray ramus communicans* back to the spinal motor nerve, and is thence distributed (Plate II). Sometimes the second (connector) fiber *passes through* the nearest sympathetic ganglion, and makes a synapse at a collateral, a plexus, or a terminal ganglion. The point of difference is that *the final synapse is always made with a cell outside the medulla spinalis.* The legend for Plate II explains some of the known details.

Autonomic afferent neurones in the thorax, loin and pelvis have their cell bodies in the posterior root ganglia. In the cranial outflow they have their cell bodies in the homologous cranial ganglia. Peripherally they supply without interruption or relay the involuntary structures, and centrally they make synapses with autonomic or somatic gray cells in the brain and cord. The peripheral end-organs in the viscera and elsewhere are of various histology. Many of the details have not been worked out. Some curious ones are recorded, such as the afferent fibers from the Pacinian bodies in the cat's mesentery.

Any bundle or trunk of peripheral nerve fibers may (though not all do) carry both autonomic and somatic nerve fibrils. In microscopical cross-sections of nerve trunks Gaskell (1886) was able to identify autonomic nerve fibrils by their extremely small diameter (averaging about 3 μ). Using this method of distinction (Fig. 6) he showed that at the neck and loin the spinal nerves are somatic; above, below and between these regions the nerve trunks are a variable mixture of the two sizes of fibrils. The vagus is, for example, almost entirely an autonomic nerve.

In the neck the three large autonomic ganglia connect with the spinal nerves by gray rami. The symmetrically arranged autonomic ganglia opposite all the twelve dorsal and the first and second lumbar vertebræ send each a gray and white ramus communicans to the adjacent spinal nerve. The second, third and fourth sacral spinal nerves have gray rami, but the homologous white rami run directly into the pelvic plexuses. The subjoined figure (Plate III) makes these facts plainer. Many details are still unsettled.

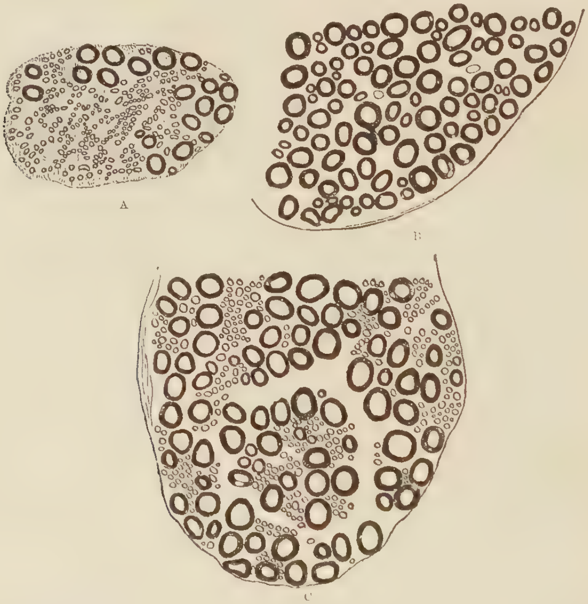


Fig. 6.—Cross-sections of roots of various nerves in dog, showing varying caliber of constituent fibers. (Gaskell.) *A*, one root of spinal accessory; *B*, first cervical anterior root; *C*, second thoracic anterior root.

Special Functions.—The autonomic nervous system may be said generally to influence, by motor and inhibitory fibers, all the functions of the body not under the control of the will. These are manifold (Plate IV), and include the operations of such diverse structures as the heart, the pupil of the eye, the arrectores pilorum muscles, the smooth muscle of the alimentary canal, bladder and genital organs and of the bronchi and bloodvessels; also all the external secretions of the body—sweat, tears, digestive juices, urine and the rest. The internal secretions likewise have intimate relations with the autonomic system. Ductless glands do not apparently depend on nervous action alone. We have already mentioned the existence (Chapter I) of chemical messengers. But we do not yet know whether the chemical messengers may not at least sometimes act through the nerve supply.

Not only the efferent but the afferent autonomic nerves (remembering that afferent autonomic nerves are really somatic in their central connections) carry on operations of prime importance. Some of these may reach the surface of consciousness, like hunger, thirst, fatigue, nausea, visceral pain; many more act subliminally, making reflex arcs in the spine without getting higher. Blood-pressure, the heart-beat, sweating, the regulation of temperature, the rhythmic movements of the bowels go steadily on through sleeping and waking hours. These stimuli are *visceral.*

It must be also noted that innumerable autonomic efferent impulses and responses are originated not only by visceral stimuli that we know nothing of, but by *sense perceptions* fully in the field of consciousness. The sight of a rattlesnake "starts the sweat" in an unprotected victim. The smell of good food makes the hungry man's "mouth water." One look at a hostile dog raises the cat's hair. When Hamlet (Act III, Sc. 4) sees the Ghost, the Queen cries in amazement:

> ". . . Alas, how is't with you
> That you do bend your eye on vacancy
> And with the incorporal air do hold discourse?
> Forth at your eyes your spirits wildly peep;
> And as the sleeping soldiers in the alarm,
> Your bedded hair, like life in excrements,
> Starts up, and stands on end."

Imagined objects may also produce the same autonomic effects as those actually perceived. The mental image of a friend soon to be seen makes one's heart beat faster. The sentimental novel reader weeps over the sorrows of a fictitious heroine. By practice it is possible to produce by way of the imagination an apparently voluntary movement of an organ under autonomic control. By this mental device, so it is said, the accomplished actress can blush at will, or dilate her pupils, merely by thinking of the physical objects that would normally produce this effect. The result in most cases is probably not a true voluntary act. But one should not make the statement too absolute. Langley remarks:[1]

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[1] Loc. cit., p. 26.

"Apart from any special emotion some people can by effort of will cause contraction of the involuntary unstriated muscle of the skin, and others can cause acceleration of the heart. . . Cases are recorded of voluntary inhibition of the heart and contraction of the pupil."

Sympathetic and Parasympathetic Antagonisms.—An important fact has been noted by Langley that when sympathetic and parasympathetic nerves are both supplied to the same organ their action is antagonistic (see details of Plate IV). We therefore have in many known instances a difference in function corresponding to the difference in origin between the two systems. For example, the sympathetic dilates the pupil; the parasympathetic contracts it. The sympathetic hurries the heart; the parasympathetic (vagus) slows it up. But there are many organs which seem to be supplied by the sympathetic only; and particularly in respect of the ductless glands present knowledge of sympathetic and parasympathetic control is fragmentary.

W. B. Cannon[1] has attempted to generalize upon the known facts, suggesting that the cranial and sacral (parasympathetic) nerves are anabolic, promoting rest and comfort, while the sympathetic is catabolic, providing for the free and even explosive expenditure of energy when occasion arises. This hypothesis awaits further research.

In sufficient pharmacological doses the secretion of the adrenal medulla, epinephrine (see Chapter VII), is "sympathico-tonic," that is, it will produce almost all the effects that electrical stimulation of the sympathetic nerve endings will produce. This has led certain authors to affirm on *a priori* grounds that there must be also a hormone which acts antagonistically to epinephrine and stimulates the parasympathetic system, producing "vagotonia." Eppinger and Hess[2] have been the chief proponents of this theory. They have called this hypothetical hormone "autonomin," and it is also alluded to in the literature as "hormone X." No such hormone has been found. In the light of the present-day views of the action of epinephrine, it seems highly improbable that such a hormone exists.

Tonus.—A brief note on tonus must be made. The autonomic nervous system seems concerned in some essential way with the *tonus*, or, as Sherrington has preferred to call it, the *posture* of skeletal muscle. This question has become of great clinical interest, since the work of N. D. Royle and J. I. Hunter[1] has indicated that certain cases of excessive muscular tonus (spastic paralysis) of the limbs are relieved by cutting the proper ramus or rami of the autonomic nerves supplying the spastic region. The complete solution of the problem of tonus is, however, still distant. Other references to recent literature may be found in the notice of the subject by Bayliss.[2] A fuller discussion of the matter is outside the limits of the present sketch.

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[1] Bodily Changes in Pain, Hunger, Fear and Rage, New York, Appleton, 1915.

[2] Die Vagotonie, Eine klinische Studie, vol. **9**, **10** of Von Noorden's Sammlung klinischer Abhandlungen, Berlin, Hirschwald, 1910.

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[1] Med. Jour. Australia, January 26 and September 27, 1924; references.

[2] Loc. cit., p. 540 (p. 21 of this book).

CHAPTER III.

BASAL METABOLISM.

Introduction, History and Literature.—The special interest that basal metabolism has for students of thyroid disease justifies a short account of the modern theory and methods. The literature of the subject is large, and is rapidly growing. References to most of it may be found in the recent study by E. M. Du Bois.[1] In a recent conversation with Dr. Bu Bois the writer was told that 90 per cent of the modern knowledge of the subject has been furnished by Magnus-Levy. But no American would wish to forget the value of the contributions made by Dr. Du Bois himself, by C. G. Benedict, Graham Lusk, W. O. Atwater and J. H. Means, not to mention a dozen or more other authors and students as well.

Definitions.—In physiology *metabolism is chemical change as it occurs in the organism.* Coal in a fireplace burning to carbon dioxide is chemical change, but not metabolism. Carbon in the body burning to carbon dioxide is a metabolic phenomenon. *Basal metabolism* is the minimal amount of chemical change consistent with the maintenance of the ordinary vital functions, and is to be measured only in the fasting and resting subject. *Measurements* of chemical action are based on heat production. The unit of heat production is the *great calorie* of chemists (commonly called in physiology "calorie") which is the amount of heat required to raise 1 kg. of water from 0° to 1° C. In theory basal metabolism, or basal heat production, is caused only by secretion, by heart beat, by respiratory movement, by involuntary muscle action and by the mental operations of a waking but unexcited brain. All voluntary movements are to be excluded during the test period, and twelve to fourteen hours should have elapsed since the last meal. The subject is tested in a comfortable reclining posture.

The basal heat production may be directly measured in a *calorimeter,* or indirectly estimated by measuring the end-products of oxidation (together with the urinary nitrogen) collected during a given period. The former is called *direct,* the latter, *indirect calorimetry.*

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[1] Basal Metabolism, Philadelphia, Lea & Febiger, 1924.

Direct Calorimetry.—Direct calorimetry is done to-day in a *calorimeter chamber.* Heat leaves the body by evaporation of water from skin and lungs, by radiation and by conduction. The chamber is built so that there is no loss of heat through its walls. The heat lost by radiation and conduction is taken up by a continuous stream of water which circulates through copper pipes in the chamber. The amount of heat absorbed by the water is estimated by measuring the total amount of water passed through and noting the difference in temperature between the ingoing and outcoming streams. The water eliminated from lungs and skin is collected by running the air of the chamber through sulphuric acid, and noting the increase of weight. This water vaporized would contain as latent heat the heat the subject has lost by evaporation. The sum of the heat eliminated by radiation, conduction and evaporation is the figure desired.

The *respiration calorimeter* is not only a direct calorimeter, but has additional apparatus for measuring oxygen absorbed and carbon dioxide given off during a given period. It thus combines direct and indirect calorimetry. Fig. 7 shows the respiration calorimeter in use at the Russell Sage Institute of Pathology, New York. It is fully described by Riche and Soderstrom.[1] It is of considerable complexity, and requires close attention from two and sometimes three persons during its operation. As it is also expensive, constructed with difficulty, and not portable, it is fortunate that indirect calorimetry has been found not only much less troublesome and circumstantial, but also nearly as reliable.

Indirect Calorimetry. C. G. Benedict[2] has described an apparatus commonly called the *Benedict unit apparatus.* The subject wears a mask, nose-piece, or mouth-piece, and rebreathes air from a closed system. The carbon dioxide is absorbed by soda lime, and the loss of oxygen is indicated by the movements of a hollow bell. Consumed oxygen is replaced by known amounts of oxygen admitted by a valve from a tank. There is a blower to keep the air in the enclosed space in motion. By properly weighing the O and CO_2 the heat production follows. A portable unit apparatus has been also devised, and there are several dealers who have imitated it by unauthorized modifications.

The "closed system" is objectionable in many ways. The

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[1] Arch. Int. Med., 1915, 2, **15**, 805.

[2] Deutsch. Arch. f. klin. Med., 1912, **107**, 156.

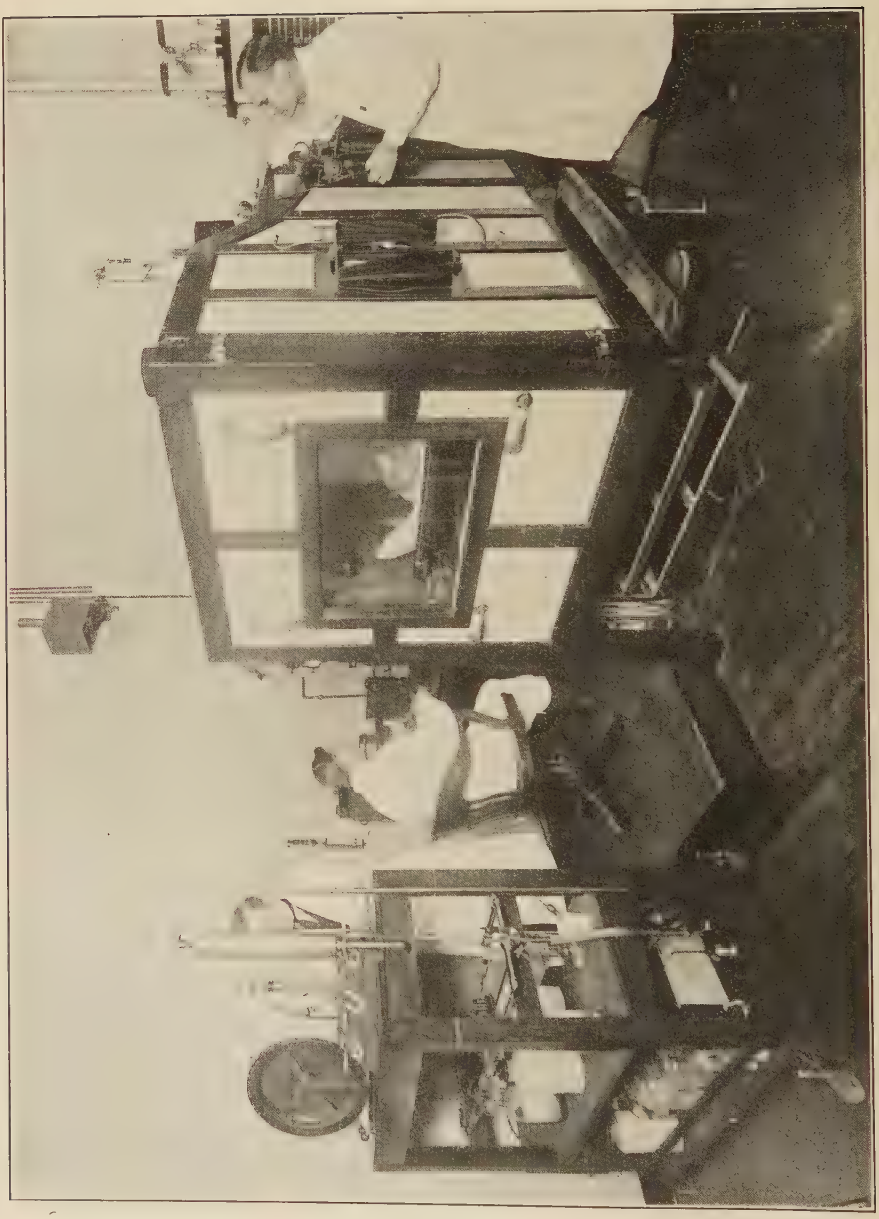

FIG. 7.—The respiration calorimeter of the Russell Sage Institute of Pathology. (Du Bois.)

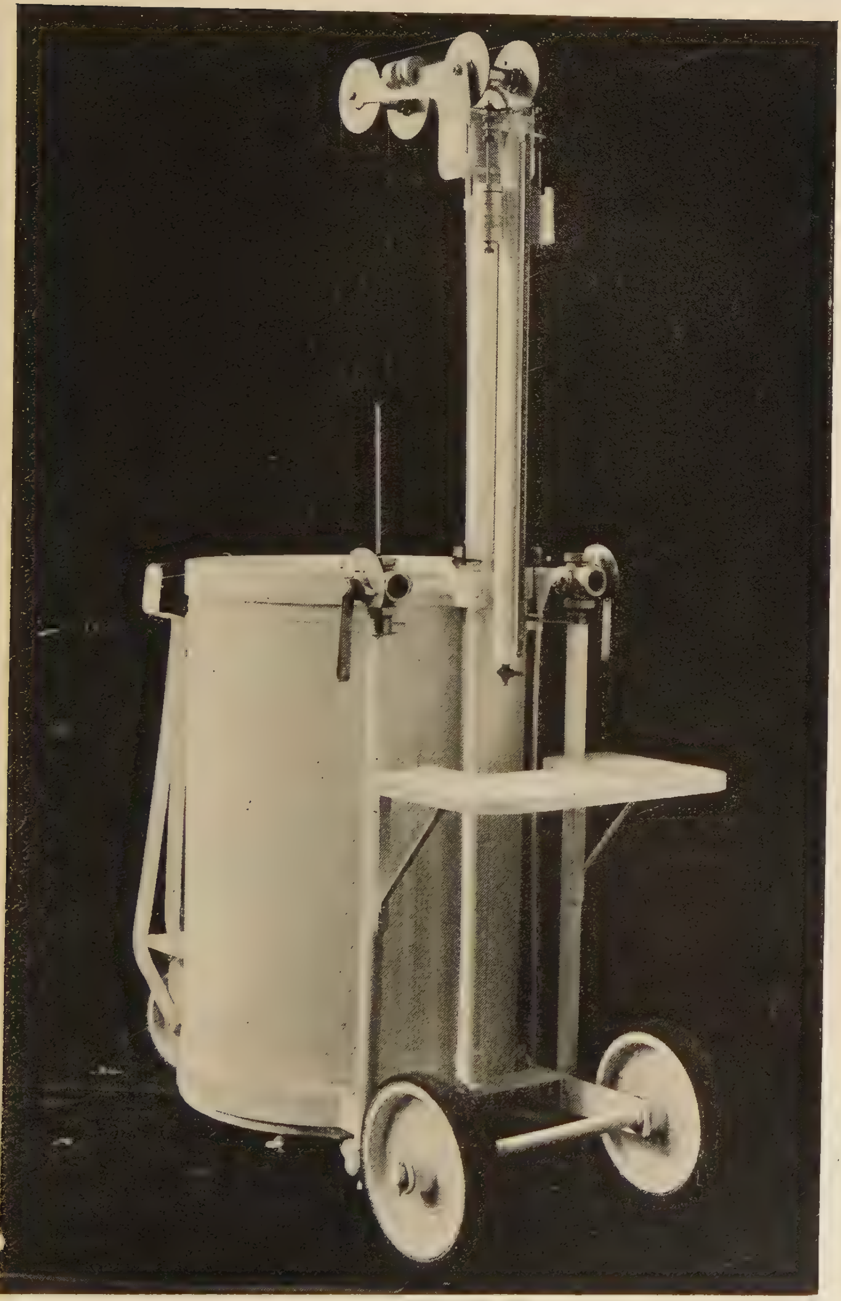

FIG. 8.—Tissot gasometer, mounted. (From Boothby and Sandiford, Basal Metabolic Rate Determinations, W. B. Saunders Company, Philadelphia.)

rebreathed air is undesirable. Patients later than the first are exposed to infections. The oxygen produces fires. The absorbing chemicals have to be changed rather often.

There are also "open methods." By Boothby and Sandiford[1] the Tissot gasometer (Fig. 8) is used with a special mask (Fig. 9), and an elaborate and rather difficult technique. J. T. King, Jr.,[2] has suggested the measurement of the CO_2 elimination only, instead of the oxygen absorption (Fig. 10). This greatly simplifies the procedure, but one has to be sure that the patient, by forced breathing, does not "wash out" more CO_2 than he has formed during the test period. Du Bois[3] also notes that this method fails to collect the CO_2 eliminated from the skin. In a number of

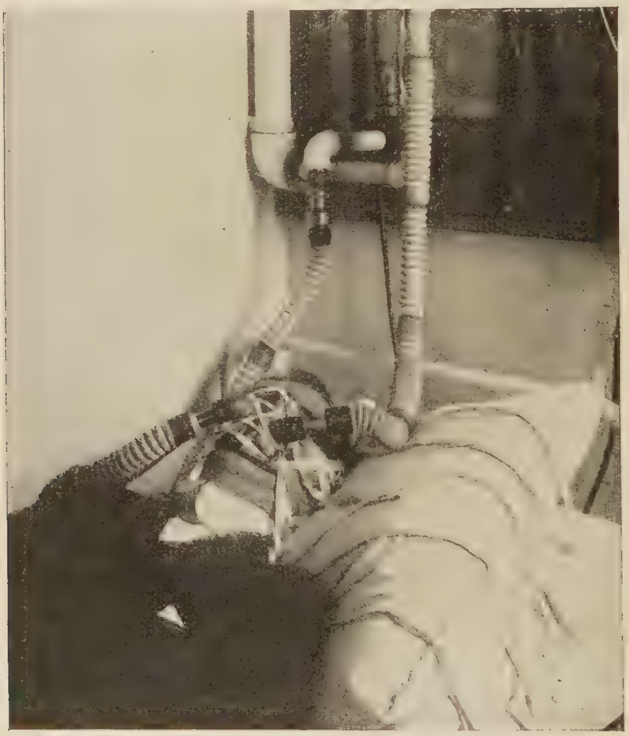

FIG. 9.—Face mask, with tapes. (From Boothby and Sandiford, Basal Metabolic Rate Determinations, W. B. Saunders Company, Philadelphia.)

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[1] Basal Metabolic Rate Determinations, W. B. Saunders Company, Philadelphia, 1920.

[2] Bull. Johns Hopkins Hosp., September, 1921.

[3] Loc. cit., p. 32.

cases I have found it very convenient for rapid clinical estimates; when three or four determinations come out with a difference of not more than 3 or 4 cg. of CO_2 per test one may feel fairly satisfied with the result. For scientific laboratory estimates the large stationary apparatus operated by experienced specialists should be alone used.

Calculations.—One must, of course, have a *unit of surface measurement,* for patients are of many sizes and weights. The unit of body surface has been chosen as 1 square meter, and all tables and calculations are based on the heat elimination per square meter per hour.

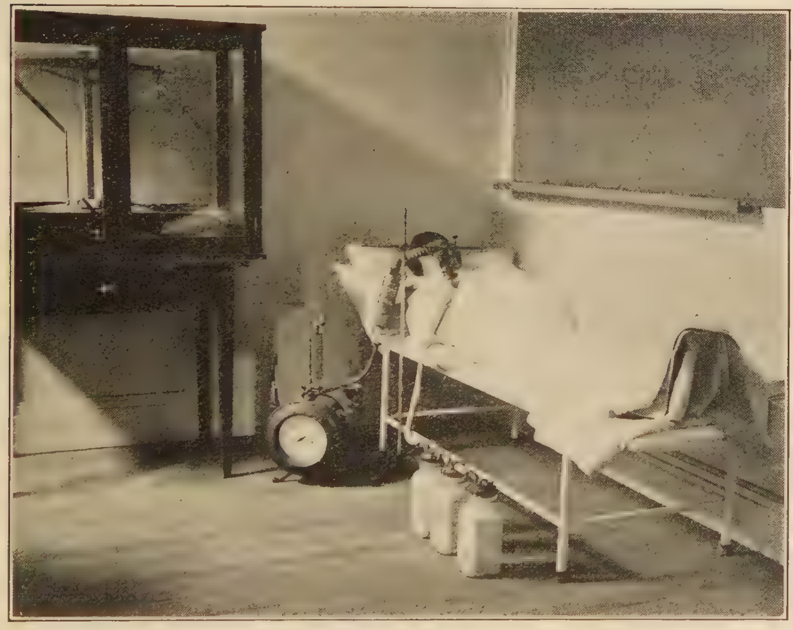

FIG. 10.—Apparatus and balance for measuring carbon dioxide elimination. (John T. King, Jr.)

The determination of the *surface area of the human body* has been attempted by various formulæ. B. Du Bois and E. M. Du Bois[1] devised a logarithmic formula which is remarkably accurate:

$$A \text{ (Surface)} = W^{0.425} \times H^{0.725} \times 71.84.$$

W is weight in kilograms and H is height in centimeters of the subject. The figures are constants, apparently found by the method of trial and error. This formula is said to be correct to

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[1] Arch. Int. Med., June, 1916.

±1.5 per cent, and is now generally used. To save the constant use of logarithmic tables the same writers have worked out all possible combinations on a very convenient *Chart* (Fig. 11). On this, with the weight and height given, the surface area may be read off at once. For example, a man 170 cm. tall, and weighing

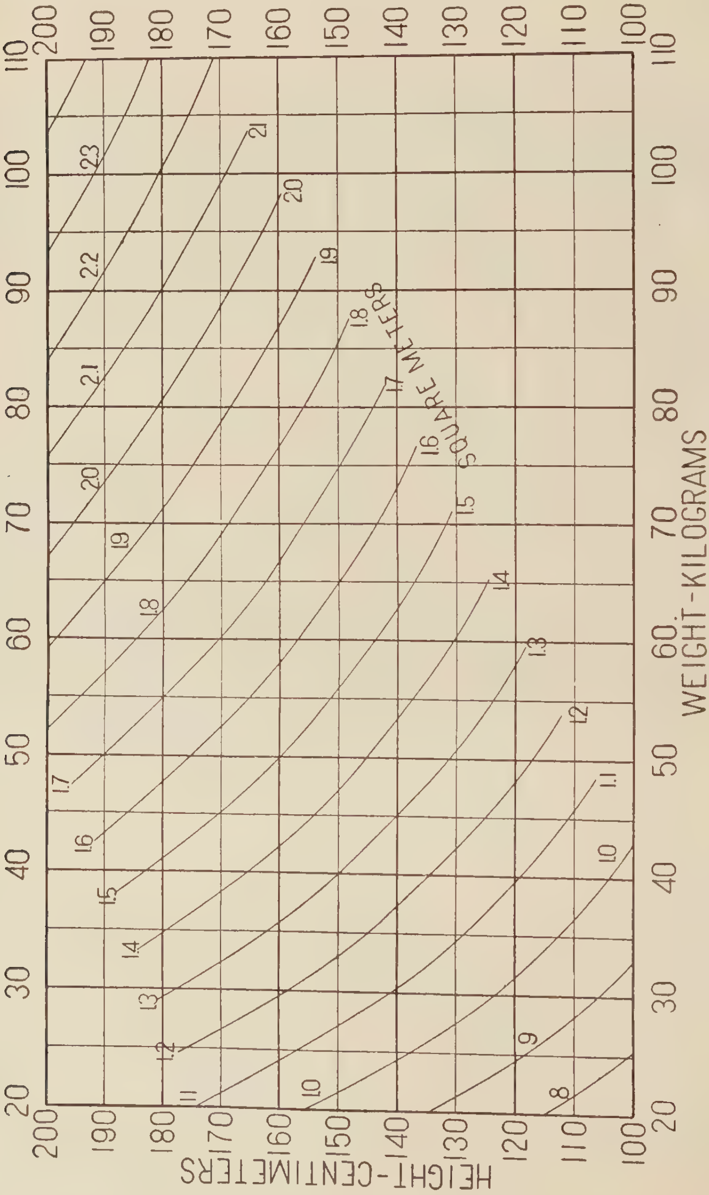

Fig. 11.—Chart for determining surface area in man from weight in kilograms and height in centimeters. (Du Bois.)

60 kg., would have a surface area of 1.7 sq. m. Average determinations of oxygen absorption in health per square meter per hour have been compiled in tables by Aub and Du Bois, and for CO_2 elimination by J. T. King, Jr. The figures are arranged in columns for various ages and the two sexes. The correctly computed figure for any new patient is checked against the average figure, and the percentage above or below the average, which is taken as 100, is used as a short designation of the result. For example, a patient with Graves's disease may be found to have a basal metabolic rate (contracted usually to the initials B.M.R.) of +35 per cent. One suspected of myxedema might be found to have a basal metabolic rate of −20 per cent.

Precautions.—Certain reasonable precautions are needful to secure a reliable result. The patient should eat a light evening meal, go early to bed and be tested before breakfasting. Before the test is made he should rest comfortably in a reclining position for about one-half hour. He should not go to sleep, neither should he be alarmed or excited. To give assurance of this the pulse, temperature and respiration should be tested before and during the test. Duplicate tests are very desirable, especially with nervous patients, new apparatus and inexperienced assistants. All results must be interpreted from a broad standpoint of clinical knowledge and experience, for the basal metabolic rate is but one factor in the diagnosis. Individual variations are normal within wide limits, just as normal temperatures range between 1° and 2°. While periodic tests of one patient may be fairly comparable with one another, figures for a new patient can be checked only against a general average of supposedly normal persons of the same age and sex. In my experience the widest range occurs in women after the menopause; this appears also to have been noted by others.[1] A normal range of 5 or 10 per cent above or below the averages is probably allowable.

Clinical Value.—It has been found that fever, various blood diseases, pituitary diseases and thyroid diseases alter the basal metabolism. The first two troubles may be ruled out by ordinary clinical tests. Pituitary disease also can be often suspected from clinical appearances. Consequently, when a basal metabolic rate determination is more than ten points off normal in a case negative for the other disorders mentioned, one is justified in suspecting thyroid disease. But neither this proposition nor its converse can be accepted as an invariable rule. The matter will be frequently mentioned in following chapters.

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[1] Crile and Associates: The Thyroid Gland, Philadelphia, Saunders, 1922.

CHAPTER IV.

THE THYROID GLAND.

Meaning of the Word.—The name is ancient. The word is also written *thyreoid,* which is a more exact form of the Greek, θυρεός, shield, the ending, *-oid*, having its usual sense. The thyroid gland is not itself a shield, but is named for its proximity to the thyroid or shield-shaped cartilage enclosing the larynx.

Synonyms are familiar.

ANATOMY.

Structure and Relations.—In man the thyroid consists of two *lateral lobes* buried in the neck, one on either side of the trachea and larynx, and generally (not always) connected by an *isthmus.* The gland lies at the level of the last three cervical vertebræ. The isthmus is a thin mass connecting the lower third of each lobe with its fellow and is adherent to the second and third rings of the trachea. In a thin, long neck the isthmus is often visible and always easily palpable. It may be identified even in a short fat neck as a soft transverse mass (just under the cricoid ring) which slips up when the patient swallows.

The *lateral lobes* are somewhat conical in shape and are convex on the outside surface. They are a little hollowed on the interior aspect, where they lie close to the thyroid and cricoid cartilages. The average weight of the adult thyroid is about 25 to 30 gm. (1 ounce). In women it is relatively a little heavier, and becomes somewhat enlarged during menstruation and pregnancy. A third (*pyramidal*) lobe frequently extends upward from the isthmus (occupying here the site of the thyro-glossal duct), or from the right or left lateral lobe. Exceptionally the gland assumes many queer and atypical shapes, without any apparent damage of function (Figs. 12, 13 and 14).

Small *accessory* or *supernumerary thyroids* are also found anywhere around or above the principal mass. Larger masses of thyroid tissue have also been found in various atypical places about the body. A lingual thyroid is not uncommon. Curious instances are recorded where minute bits of normal-looking thyroid have been found at autopsy scattered through the entire body, apparently carried thither by the vessels accidentally after injury to the primary gland, or as supposed by some,[1] as metastases of a thyroid adenoma. An *intrathoracic thyroid* may be an accessory gland, or an extension or displacement of the main gland into the anterior mediastinum.

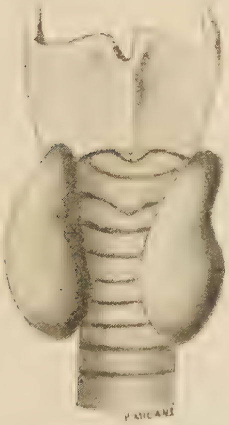

FIG. 12.—Thyroid without isthmus and without pyramidal process. (Crotti.)

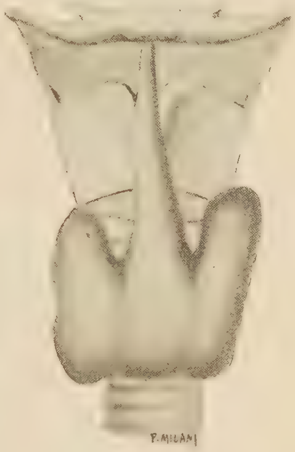

FIG. 13. — Thyroid with one pyramidal process. (Crotti.)

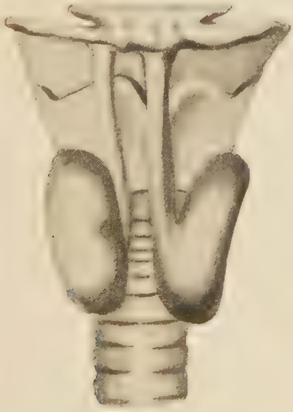

FIG. 14.—Thyroid with two pyramidal processes. (Crotti.)

Vessels and Nerves.—The vessels of the thyroid are numerous. The superior and inferior thyroid arteries are large and anastomotic. Venous and lymphatic plexuses are abundant. The *nerve supply* is said to be derived exclusively from the sympathetic system (middle and inferior sympathetic cervical ganglia). So far as I can find from the literature, the parasympathetic sends no fibers to the thyroid.

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[1] Ewing, J.: Neoplastic Diseases, 2d ed., Philadelphia, Saunders, 1922. Ewing thinks the evidence entirely insufficient to prove that a normal gland even behaves in this way.

The Thyroid in Other Animals.—*Cat.*—In the cat there is no thyroid isthmus. The two lateral lobes are, however, homologously situated in the neck as compared with man. The parathyroids are closely adherent to the cat's thyroids. Accessory thyroids are probably numerous in view of the close resemblance of the cat's glands to the dog's in other ways.

Dog.—As in the cat there is no thyroid isthmus, and the parathyroids adhere closely to the thyroid lobes. Accessory glands are numerous in the dog. Thanks to the painstaking researches of W. S. Halsted,[1] it has been shown beyond doubt that bits of thyroid of the size of a pin-head, and larger, occur around the main thyroids in the neck of the dog, and in the anterior mediastinum all the way to the pericardium. It is therefore, as a rule, impossible to produce postoperative myxedema in dogs. They may die of parathyroid tetany, but after a thyroidectomy which leaves the parathyroids physiologically intact, dogs are, as a rule, just as well as before, and they stay well for months and years, unless they are starved, mishandled or contract some intercurrent disease. "Loss of hair," so often mentioned, is usually due to mange, a common scourge of kennel dogs. Exceptionally, of course, canine myxedema may occur. It is a rare accident. In the operative experience of many years I have never seen it.

Rabbits.—Rabbits have a thin lobe on each side and a very thin isthmus. Thyroidectomy is troublesome because of the peculiarly intimate relations of the lateral lobes to the recurrent laryngeal nerves. If one of these is wounded the animal is apt to die of asphyxia from paralysis of the vocal cords. As in dogs, thyroidectomy has no effect; presumably the cause is the same—accessory glands.

In respect to the *smaller rodents* there is little information.

Monkeys.—The thyroid may or may not have an isthmus. The parathyroids are four. Vincent and Jolly[2] report that the parathyroids are sometimes buried in the thyroid. Horsley seems to have had remarkably good luck (p. 46) with his experimental animals. As to accessory thyroids in monkeys information is scanty.

Development.—Like the other glands along the alimentary canal the thyroid develops as an epithelial cup. It is first noticeable in the embryo about the end of the fourth week as a dimple on the floor of the pharynx. The dimple develops into a tube which slowly elongates caudally, forks and finally divides into a series of cellular cords. The canal or diverticulum connecting the gland with the pharynx is called the *thyro-glossal duct.* The duct presently atrophies for most of its extent, cutting off the gland from the pharynx, but a small part of the pharyngeal end persists as the *foramen cæcum* of the tongue.

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[1] Bull. Johns Hopkins Hosp., 1896, **1**, 373.

[2] Jour. Physiol., 1904, **32**; 1906, **34**.

Fine Structure.—Under the microscope the thyroid is found to consists of ovoid pockets, or alveoli, containing a structureless, eosin-staining "colloid" (Greek, κόλλα, glue), and lined with a single layer of cubical or flat epithelium, resting on a basement membrane of connective tissue (Fig. 15). Vessels are numerous. The lymphatics may contain masses of the same colloid found in the alveoli. The gland-like appearance of the thyroid long ago roused the curiosity of anatomists, and the absence of a duct was for years a mystery.

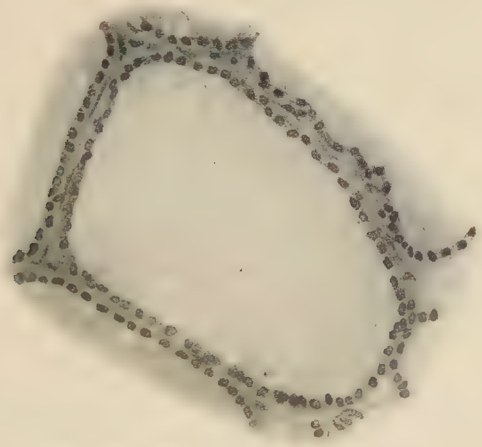

FIG. 15.—Thyroid colloid with vacuoles. × 350. (Crotti.)

PHYSIOLOGY OF THE THYROID.

Progress of Knowledge.—In respect of the thyroid secretion and its action in the animal economy the progress of knowledge has been slow. Sir Astley Cooper, in the eighteen twenties, is said to have attempted experimental thyroidectomy in animals, but to have desisted from fear of excessively exciting the prejudices of the antivivisectionists. In 1856 Moritz Schiff,[1] of Frankfort-on-the-Main, found that one dog and several white rabbits, rats and guinea-pigs survived thyroidectomy, but that several more died some days after the operation, with symptoms apparently of nothing more than depression and somnolence. The publication of this observation seems to have passed unnoticed.

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[1] Rev. méd. de la Suisserom., 1884, **4**, 65. Schiff here summarizes his original report (Untersuchungen über die Zuckerbildung in der Leber, Würzburg, 1859) which I have not seen.

Claude Bernard recognized the gland as a gland of internal secretion (see Chapter I), but in his last work[1] he writes: "L'anatomie descriptive, l'histologie du corps thyroïde, la connaissance de ses vaissaux sanguins et lymphatiques, ne sont elles pas aussi complètes que pour d'autres organes? . . . Et cependant nous ne savons absolument rien sur les usages de ces organes. Nous n'avons pas même idée de l'utilité et de l'importance qu'ils peuvent avoir."

The thyroid problem was, however, nearing a solution before this was written. In 1873 Sir William Gull[2] read a paper before the Clinical Society of London, called "On The Cretinoid State Supervening in Adult Life in Women." This paper marked a distinct advance in the conception of cretinism. Cretinism had been long known as a congenital affection, but was at that time said not to occur after the fourth or fifth year, though Gull notes 1 case reported by Hilton Fagge[3] which began at the eighth year in a previously normal child.

Gull's cases were 5 in number, 3 only alluded to and 2 fully described. He seems to have thought it significant that all his patients were women, but his descriptions are admirable. One case was as follows:

"P. M., a married woman, aged forty years, having had five children, and living in good circumstances, came under my observation in 1866, complaining of general languor.

"Heat [temperature?] was normal; pulse, 60. Catamenia too profuse. There had been gradual and general increase in bulk. The features had become broad and flattened, the skin was peculiarly fair and fine and soft, with a very delicate rose bloom on the cheeks. The cellular tissue about the eyes was thrown into folds, giving the impression when cursorily looked at of being edematous. The eyes were bright; the lips thickened, and of a light rose-purple. Tongue large; the speech guttural . . . as if the tongue were rather unwieldy. The sounds and impulses of the heart were normal, breathing was normal, urine normal. . . . This change continued to advance, and in 1873 I made the following notes: Lips large, thick. . . . Features broad. . . . Skin and subcutaneous tissues lying in resisting folds. Hands broad and spade-like, the textures suggesting edema, but not pitting. . . Mind generally placid and lazy, but liable to being occasionally suddenly ruffled. Heart's action and breathing normal. Urine normal. Catamenia continues rather profuse." He adds that the thyroid was not enlarged in his cases, but from the thickness and fulness of the skin he could not say exactly what the condition was. He notes further, "It will be noticed that I have designated this state cretinoid. My remarks are rather tentative than dogmatical. . . . That it is allied to the cretin state would appear from the form and features, the changes in the lips and tongue, the character of the hands . . . and the peculiarities, though slight, of the mental state; for although the mind may be clear and the intellect unimpaired, the temper is changed."

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[1] Leçons de physiologie opératoire, Paris, 1879, p. 294.

[2] Clin. Soc. Trans., 1874, **7**, 180.

[3] Medico-Chir. Trans., 1871, **54**, 155.

W. M. Ord[1] first introduced the name *myxedema* for the new disease, and also reported 5 cases, all in women. In an autopsy in 1 he found the subcutaneous tissue not dropsical, but "filled with a gelatinous or mucinoid substance," which suggested the new name. He reported the thyroid as "practically annihilated," but thought this a secondary shrinkage due to pressure.

"So far," as Stephen Paget remarks in his interesting story,[2] "the problem was insoluble, for nobody knew what the thyroid gland was for. Men hesitated to call it a gland; they called it the thyroid body." However, the theory was growing to a point of intelligibility. About this time A. and J.-L. Reverdin,[3] and Kocher[4] brought forward reports of some strangely unfortunate results following the new operation for extirpation of goitrous thyroids. By comparison with the recent English reports, it soon became evident that cachexia strumipriva, "myxœdème opératoire," cretinism and clinical myxedema were identical conditions. To quote again from Paget:[5] "On December 14, 1880, the Clinical Society of London appointed a committee to investigate the whole subject. Ord was chairman, Hadden was honorary secretary and Horsley a member of the committee."

Schiff[6] contributed some valuable additional observations at this time, and Horsley's paper,[7] giving accounts of the production of experimental myxedema in animals, offered a final solution of the clinical problem of myxedema. In 1888 the full report of the committee for the Clinical Society was published, substantiating the well-known facts of our day.

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[1] Medico-Chir. Trans., 1878, **61,** 57.

[2] Victor Horsley, Study of His Life and Work, London, Constable & Co., 1919.

[3] Rev. méd. de la Suisse rom., 1883, **3,** 169.

[4] Langenbeck's Archiv, 1883.

[5] Loc. cit.

[6] Rev. méd. de la Suisse rom., 1884, **4,** 65, 425.

[7] Brit. Med. Jour., January 17, 1885.

Thyroid gland as a therapeutic resource in myxedema began to be used about the same time, though nothing seems to have been tried at first except grafting (Schiff, Kocher and others). Early in the nineties fresh thyroid *per os* was tried. By 1893 desiccated thyroid began to appear in the price lists of drug dealers.

It is rather remarkable that the experimental thyroidectomies of the eighties on animals should have been so productive of correct scientific results, for the parathyroids were then but little understood, and in many of the operations they were unwittingly removed, mixing the picture of acute parathyroid tetany with the much slower metabolic changes of myxedema. Horsley's choice of monkeys was fortunate. The Clinical Society's committee correctly attributed the occasional failures to faulty technique or the presence of accessory glands.

CHEMISTRY OF THE THYROID SECRETION.

Iodine.—As the clinical importance of the thyroid secretion became more evident, the studies of physiological chemists were intensified, and analyses, qualitative and quantitative, began to appear. Their object was twofold—science demanded a solution of the chemical problem and clinicians demanded a more satisfactory medicament. But the analytical methods of the time were inadequate. Numerous announcements of various kinds were made, but were unconfirmed, and now require no notice.

Owing to the long-known and successful clinical use of iodine in many cases of goitre, Kocher is said[1] to have suspected its presence in the thyroid and to have suggested to one of his assistants the making of analytical tests for iodine in thyroid material. These failed. Eugen Baumann, of Freiburg, shortly before his death, in November, 1896, first found iodine in the thyroid. Partly in collaboration with his assistant, E. Roos,[2] he announced the isolation of a thyroid derivative which he called *thyroiodin* (also later called *iodothyrin*), and which contained 2 to 10 per cent of organically combined iodine and 0.5 per cent phosphorus. The name and process were patented at that time by a German firm. Clinical tests in cases of myxedema were positive.

The quantitative methods devised by Baumann for the determination of iodine in organic combination were greatly improved by Riggs[1] and by Andrew Hunter.[2] Hunter's process is not very long or very hard, and is quite accurate. Essentially it requires the oxidation in a nickel crucible of a weighed amount of dried gland with a mixture of carbonates. This converts the iodine to iodate or periodate, which by an additional process is titrated. E. C. Kendall modified Hunter's methods to a certain extent, but so far as I am informed, Hunter's process is still in favor in most laboratories.

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[1] Crotti: Thyroid and Thymus, 2d ed., Philadelphia, Lea & Febiger, 1922.

[2] Ztschr. f. physiol. Chem., 1896–1897, **21**, 19, 319, 481; **22**, 1.

Reid Hunt's[3] analyses of the percentage of iodine in the dried thyroids of various mammals were useful and timely. Hunt's table[4] follows:

Small children	0
Maltese kid	0
Dog	0.061
Guinea-pig	0.050
Sheep	0.176
Bullock	0.250
Human (goitre)	0.040
Human	0.23 to 0.26
Hog	0.330

Sheep's gland probably owes its iodine deficiency to the frequent cystic and fibrous enlargements which it shows. Individual specimens of all the above of course vary; the figures are averages.

It is a curious fact that in this country all raw thyroid is richer in iodine in summer than in winter. The researches of A. Seidell and F. Fenger[5] and of F. Fenger[6] have been generally confirmed as to this point. The glands were collected in large numbers in Chicago stockyards from animals coming from all the States. Percentages of iodine in dried and fat-free bullocks' thyroids ran thus:

1911.		1912.		1912.	
Sept. 1	0.286	Jan. 7	0.109	May 12	0.079
Oct. 1	0.242	Feb. 4	0.028	June 9	0.145
Nov. 11	0.361	Mar. 3	0.058	June 23	0.192
Dec. 10	0.217	April 14	0.075	July 7	0.332
				Aug. 18	0.347

Like variations occurred in hog glands and sheep glands. In 1914 to 1917 the experiments were repeated on immense numbers of glands with similar results.

Other Inorganic Constituents.—Among other inorganic constituents arsenic is said to be present,[7] and Sophie Morgenstern[8] found by analysis calcium, sulphur and phosphorus, as well as iodine. Magnesium was also present, but seemed to be confined to glands that were evidently pathological. Fluorine, chlorine and bromine are also found, together with potassium and sodium. Many of these elements, being found in the blood, might be expected to be present in all the organs.

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[1] Jour. Am. Chem. Soc., 1909, **31**, 710.

[2] Jour. Biol. Chem., 1909-1910, **7**, 321.

[3] Jour. Am. Med. Assn., 1907, **49**, 1324. Hunt and Seidell, loc. cit., p. 53.

[4] The higher figures run almost like the percentages of blood sugar in diabetes, a coincidence which perhaps may help the memory.

[5] Jour. Biol. Chem., 1912–1913, **13**, 517.

[6] Endocrinology, 1918, **2**, 98.

[7] Crotti: Loc. cit.

[8] Arch. f. Anat. u. Physiol., 1912, Ergänzungsh., p. 259.

Organic Constituents.—*Proteins.*—The usual methods for dealing with proteins show that if fresh thyroid tissue be rubbed up with sand, shaken with slightly alkaline physiological saline solution and allowed to stand (some antiseptic being added), a large part of the cellular constituents is dissolved. The opalescent solution resulting after filtration contains a complex of mucin bodies, nucleoproteins, globulins and albumins. On slight acidification with acetic acid the so-called nucleoproteins fall in an abundant flocculent mass, leaving the globulins and albumins, which may be later salted out in the usual way. Of these precipitates globulins and nucleoproteins have been used to a certain extent in clinical work (p. 113), but have never been popular. They are complex mixtures and their precise formula is of course unknown. They contain the blood and tissue proteins common to the species as well as those peculiar to the gland used. They may be standardized as to nitrogen content by a Kjeldahl determination. A. Oswald[1] emphasized the clinical effectiveness of *thyreoglobulin*, but all such work is pretty well out of date. Repeated resolution and reprecipitation probably does not clear such substances of material *adsorbed* along with the large colloid particles which come down with the change in electrical charge.

Serological studies have been limited. On p. 70 will be found an account of some complement-fixation experiments by John Koopman and myself in Graves's disease.

Nature and Action of the Iodine Compound.—From the work so far described it appears that iodine is indispensable to the physiological action of the thyroid gland. The further questions remain to be answered, What is the compound of iodine? How does it act? These questions will be considered together in the following paragraphs.

E. C. Kendall, after many years of laborious study, and a number of fragmentary reports of progress from 1910 on, offered to the American Chemical Society in Boston, September, 1917, his paper on the thyroid hormone,[2] in which he claimed to have isolated the active principle of the gland. For reasons given below he called the extract *thyroxin.*

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[1] Beitr. z. chem. Physiol. u. Path., 1902, **2**, 545; references.

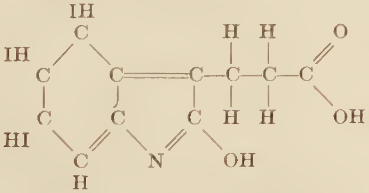
[2] Collected Papers of The Mayo Clinic, 1917, **9**, 309.

To appreciate the thoroughness and tireless industry which have characterized his work his paper should be read in full. He begins by noting that chemical study had been disappointing and that, though "thyreoglobulin"[1] has the physiological action of dried gland, no crystalline substance had been isolated from the thyroid and that no known iodine compound[2] had been found to act as thyroid extract acts; moreover, that no thyroid extract *not* containing iodine had been found active. He describes in chemical detail his earlier and later methods. As an example of the task he had set himself, he mentions that his first 18 gm. of thyroxin resulted from working up more than two tons of animal gland, "a very small percentage of the theoretical amount."

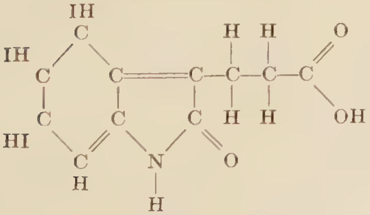
Of the *physical and chemical properties* of thyroxin he notes: "The melting-point of thyroxin is 240° C. The compound is colorless, odorless and tasteless. It is soluble in strong alkaline hydroxides, but in dry crystals is insoluble in the carbonates of the same metals." It crystallizes as curved rosettes (system not stated), needles, or sheafs of long blades. Thyroxin sulphate contains 60 per cent, and pure thyroxin 65 per cent, of iodine. The empirical formula is:

$$C_{11}, H_{10}, O_3, N, I_3$$

From a study of its derivatives he believes it to be trihydro-triiodo-alpha-oxy-indol propionic acid. Analyses showed a molecular weight of 585, corresponding to a calculated weight of 584.8. He proposed the following structural formulæ:



Structural formula of thyroxin
(alkaline solution.)



Structural formula of thyroxin
(acid solution.)

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[1] Oswald: Ztschr. f. physiol. Chem., 1901, **32**, 121.
[2] Koch, F. C.: Jour. Biol. Chem., 1913, **14**, 101.

The chemical facts bearing on the structural probabilities indicated above are fairly stated. He mentions the two tautomeric possibilities—a common occurrence in the indol families—and states his grounds for the grouping selected. "The name *thyroxin* was decided on from the evident desirability of emphasizing the presence of the reactive carbonyl group. The name 'thyroxy-indol' combines in a satisfactory manner the source of the hormone, the presence of oxygen and the mother substance indol. 'Thyroxy-indol' appears too bulky a word to stand everyday usage, and therefore has been abbreviated to *thyroxin,* which we here suggest as the name of the thyroid hormone. . . . The function of the iodine in thyroxin is to increase the reactivity and sensitiveness of the functional groups present, namely, the carbonyl and the imino. Any other function of the iodine is highly problematic.

"The fact that the compound exerts its influence in the animal organism for days after a single injection proves that it is not destroyed in carrying on its physiological action and suggests that it acts as a catalyst."

Kendall describes the effect of a single large dose in dogs as producing in twelve to thirty-six hours an increase in the pulse-rate and in the N and CO_2 elimination. This soon passes off. Maximum effects are secured by several successive daily doses. One dose of 150 mg. to a goat caused the usual effects, but subsided in three or four days. Eleven daily doses of 9 mg. each to another goat resulted in the death of the animal.

Headache, nausea and diarrhea are produced in man by large doses; small doses increase the sense of well-being and ability. Cretinism and myxedema are rapidly and remarkably benefited. "Every cell in the body responds." The effects of thyroxin equal in every way the effects of desiccated gland, resulting in virtually 100 per cent of "cures." Injection of thyroxin produces: (1) Increased output of CO_2, out of proportion to the N elimination; (2) increased N elimination; (3) increased nervous irritability and increased pulse-rate; (4) the most remarkable effect—the specific and unique effect—of thyroxin is the increase in rate of basal metabolism.

Thyroxin does all that dried thyroid does; dried thyroid can do no more. Split products of thyroid other than thyroxin produce no relief of the specific signs of thyroid deficiency.

Kendall finally states candidly, "Whether or not there is some other substance within the thyroid secretion which may be regarded as another hormone time alone can tell. It seems highly probable that the various effects secured by an aqueous or other extract of the thyroid are due to split products of protein, which though present in the thyroid cannot be considered essential to thyroid activity."

Kendall's work has been generally accepted by the medical profession. Cameron and Carmichael[1] found that large doses of thyroxin produced upon white rats and rabbits the same reduction in rate of growth and increase of size of certain internal organs that are produced by thyroid gland. They conclude that "Thyroxin answers satisfactorily all the tests to which it can be subjected, and is undoubtedly the essential chemical compound (autacoid, hormone) secreted by the thyroid gland. . . .

"Quantitatively, when compared on a basis of iodine content, the effects of thyroxin are distinctly less [than desiccated thyroid]. This is probably due to bacterial decomposition; thyroid acts as a shield." S. Vincent,[2] quoting the first and neglecting to quote the last sentence in the last paragraph above, concludes rather inconclusively, "It is clear, then, that there must be some other active principle."

The only thing to date that thyroid extract can do and that thyroxin cannot do so well is the protection of mice from acetonitrile poisoning.[3] Perhaps here also thyroxin has a chance to decompose before being *eaten* by the subject animals; but intravenous injections were found by Hunt to be also relatively inefficient.

The chemical process is the property of the University of Minnesota. E. R. Squibb's Sons now manufacture and market thyroxin under license of that institution.

Biological Studies of Thyroid Action.—*Frogs.*—J. F. Gudernatsch[4] showed that tadpoles of *Rana temporaria*, and *Rana esculenta*, fed on thyroid gland (Fig. 16) showed a remarkable tendency to rapid and premature metamorphosis, as judged by the early appearance and rapid growth of the fore and hind limbs. The tadpoles did not increase in size, they merely differentiated. Thymus feeding, on the contrary, caused parallel groups of tadpoles to increase in size, but apparently suppressed metamorphosis. The author thought the gland might be secretory in its effect, or might be neutralizing or eliminative for toxins or waste products.

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[1] Jour. Biol. Chem., 1921, **46**, 35.

[2] Secretion, London, Arnold, 1924, p. 154.

[3] Hunt, R.: Loc. cit., p. 53.

[4] Am. Jour. Anat., 1913–1914, **15**, 431; Anat. Rec., 1916–1917, **11**, 357.

This work attracted much attention in the next few years, and was everywhere confirmed. W. W. Swingle[1] in a series of subsequent experiments (Fig. 17) verified all the statements of Gudernatsch, and found further that a 1 per cent mixture of iodine crystals with wheat flour would produce the same effect as thyroid. Iodoform (less actively) and potassium iodide (least actively) behaved in the same way. The iodine-flour mixture produced prompt metamorphosis even in tadpoles deprived of their thyroids by operation.

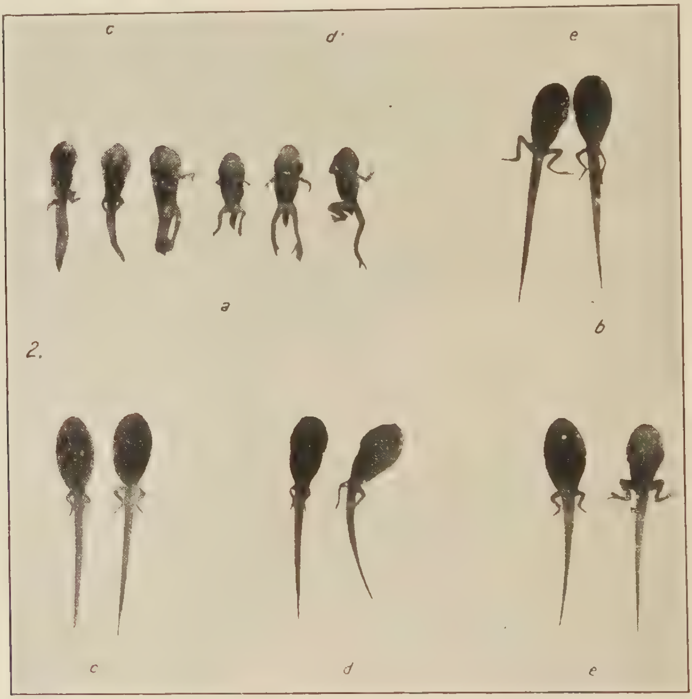

FIG. 16.—Tadpoles showing effects of thyroid feeding. *a*, tadpoles (Rana temporaria) fed on thyroid; though dwarfed in size all have metamorphosed; the tail with some has almost disappeared; forelegs well developed. *b*, tadpoles fed on thymus; *c*, on liver; *d*, on muscle; *e*, on adrenal. (Gudernatsch.)

John Rogers and co-workers[2] published some interesting experiments showing the effect of extracts of thyroid and other organs upon contractility of voluntary muscle, blood-pressure and the flow of pancreatic secretion. The conclusions reached have cleared up some obscurities in the chemical physiology of split thyroid proteins.

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[1] Jour. Exp. Zoöl., 1918, **24**, 521; Endocrinology, 1918, **2**, 283.

[2] Am. Jour. Physiol., January and June, 1915; March, 1916; January, 1918.

Acetonitrile Poisoning.—Reid Hunt,[1] and Reid Hunt and A. Seidell[2] announced that thyroid extract given to white and gray mice remarkably increases their resistance to acetonitrile poisoning.

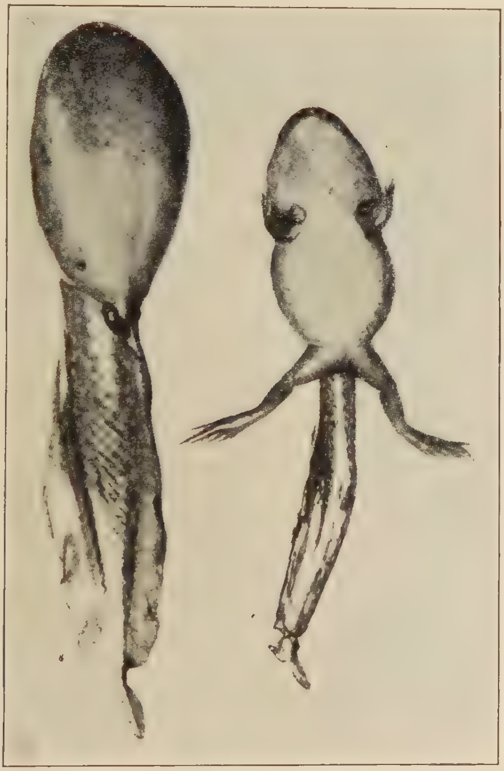

FIG. 17.—Thyroid-fed and control tadpoles (Rana catesbiana), showing effect of twenty-three days' thyroid feeding. (Swingle.)

Acetonitrile is the cyanide of methyl, CH_3CN. Hunt[3] thinks that the toxicity of acetonitrile depends immediately on its relations to the alcohol group of narcotics, and later on, to the action of its decomposition products, of which the most poisonous is HCN. "Part of this is neutralized by sulphur and excreted as thiocyanate. The methyl group appears in the urine as formate." Probably the decomposition process is one both of hydrolysis and oxidation. This author notes further in the same article:

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[1] Jour. Biol. Chem., 1905, **1**, 33.

[2] U. S. Hyg. Lab. Bull., 1908, No. 47.

[3] Am. Jour. Physiol., 1922–1923, **63**, 257; extensive bibliography on the whole question.

"It was in connection with the study of the toxic action of acetonitrile that I discovered the test for thyroid. I thought that if certain processes of oxidation in the body could be increased, the toxicity of the nitrile should be increased as the result of the freeing of a large amount of HCN. Accordingly, I administered thyroid to rats and guinea-pigs; the toxicity of the nitrile was greatly increased. But mice, both white and gray, reacted in the opposite way; they became very resistant to the poison. I have been unable to find a very probable explanation of this species difference."

Thyroid from a great variety of animals was used. The protective value of each sample varied very closely with the iodine content. The iodine percentage of any unknown sample of thyroid might be pretty exactly predicted from its protective action.

These facts have been widely confirmed. They seem to be unquestionable. Controls of the animals used were very careful. Controls of the thyroid extract with other animal proteins were innumerable. Even samples of thyroid containing no iodine discoverable by present analytical methods retain still a distinct protective power. The author infers that in the acetonitrile test we have a biological test of great value and sensitiveness in detecting small amounts of thyroid secretion.

Hunt also affirms that when thyroxin is used "The physiological action of thyroxin, both by feeding and by intravenous injection, is (expressed in terms of iodine content) less than that of thyroid."

Upon the facts just mentioned—the work of Gudernatsch, of Rogers, and of Hunt—Kendall[1] comments rather briefly, saying only that "They may or may not be related to the activity of thyroxin; at best they are minor signs of a general fundamental effect on cell activity."

In the laboratory of F. de Quervain[2] the observation of Asher and Streuli that white rats fed on thyroid are more easily asphyxiated than controls has been amplified in many interesting ways by Hara and Branovačky.

Conclusion.—The most widely accepted theory of to-day is that of Kendall, namely that the thyroid secretion acts as a catalytic substance, expediting and facilitating chemical change in all the cells of the body. Theoretically it undergoes no permanent change in this process, being a physiological "go-between;" but practically it does slowly disappear from the body, and from time to time requires renewal. Kendall's *Chandler Lecture*[1] reviews much of his previous work, and gives an elaborate and interesting but highly speculative study of the mode of action of thyroxin as a catalyst.

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[1] Loc. cit.

[2] Goitre, Snowman's Translation, Bale, Sons, and Danielsson, London, 1924, complete references.

There are still some writers who urge that the gland secretion is a "detoxicating substance." The weight of evidence to the present time is in favor of the catalytic hypothesis.

Sources of Thyroid Iodine.—The supply of iodine for the uses of the thyroid gland—a supply under normal conditions strained out or automatically selected from the circulating blood—must evidently, as in the familiar case of iron, come from food or drink, or both.

Iodine in combination is present in many parts of the earth as a constituent of the soil. It is dissolved in many natural waters, and assimilated into the tissues of many food plants and animals. Sea water contains it—combined with bases like sodium—in very minute percentage but in total amount a vast quantity. Certain sea algæ ("kelp," for example) absorb large amounts of iodine from sea water. The ash of these plants was once the cheapest industrial source of iodine.

There are, however, certain regions of the earth's surface where the soil is very poor in iodine, and the waters of such regions contain practically none. The Great Lakes region in this country is said to be poor in iodine. Glacial waters, arising directly from snow, also contain little or none of the element named, and the Swiss valleys and great tracts in India are watered entirely by glacial streams. The supposed bearing of these facts upon certain diseases of the human thyroid will become apparent in later sections of this chapter.

DISEASES OF THE THYROID GLAND.

A. TUMORS AND INFLAMMATIONS.

Primary New Growths.—Primary new growths of the thyroid may be loosely classified as cysts, adenomata, fibrous tumors, cancers and sarcomas. Their causes, pathological appearances and surgical treatment are to be found in the standard works on pathology and surgery. The present volume is meant to deal with such conditions only in so far as they are related to the secretory functions of the thyroid. Such relations will be mentioned in the following pages from time to time, as occasion arises.

Metastatic processes connected with thyroid tumors are peculiar.

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[1] Industrial and Engineering Chemistry, 1925, **17**, 525.

Cohnheim[1] and many subsequent writers have described metastatic growths from a benign colloid goitre. It is even claimed that normal thyroid may metastasize, but this is very doubtful (p. 40).

Granuloma of the thyroid is a curious condition ("Riedel's struma"), in which the gland is transformed into a bulky, hard, fibrous mass not apparently malignant, and not generally associated with secretory derangement; but myxedema is sometimes observed.

Small single and multiple *adenomata* are thought by many students to originate in fetal epithelial rests. They are sometimes associated with hyperthyroidism.

I have reported an *angiosarcoma* of the thyroid.[2] Malignant diseases of the thyroid (cancers) have been sometimes reported which were accompanied with signs of thyroid toxemia.

J. Ewing[3] describes epithelial overgrowths in the thyroid as: (1) Simple goitre, (2) Graves's disease; (3) true tumors. He adds: "These conditions are not sharply separated from each other; simple goitre may assume the character of the exophthalmic type. True tumors may develop in the course of either form. The correct interpretation of hyperplastic processes in the thyroid demands special standards dependent upon the development, structure and function of this gland and not applicable elsewhere."

Inflammations.—Among inflammations are to be mentioned abscess, primary and secondary, and the chronic productive inflammations that accompany most old goitres. Here *calcification* is also common.

Arterial Disease.—Arterial disease of the gland may be localized, or a part of a general arteriosclerosis.

B. SECRETORY DISEASES.

General Comment.—Any internal secretion may conceivably be disordered in several ways. The secretion may be: (1) Absent, (2) decreased, (3) increased, or (4) abnormal. An increased or decreased secretion and an abnormal secretion may even coincide. There are clinical, chemical and pathological grounds for believing that in the case of the human thyroid any of these conditions may singly occur; that one may in course of time follow another, and that two or more may even alternate in their clinical occurrence. Classification, therefore, of the secretory diseases of the thyroid is an elusive, difficult and artificial undertaking. I shall not attempt anything of the kind, except such an orderly arrangement of the facts as facilitates study and clinical understanding.

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[1] Virchow's Arch. f. path. Anat., 1876, **68**, 547.

[2] Presbyterian Hosp. Repts., New York, 1898.

[3] Loc. cit., p. 41.

1. SIMPLE GOITRE.

Synonyms.—Simple goitre (or goiter) is also called *endemic, sporadic* and *epidemic goitre* (not exophthalmic goitre), *bronchocele, struma thyreoidea,* and in England "Derbyshire neck," "Nithsdale neck." Many other terms enjoy a local popularity. The word goitre comes through the French *goître* from the Latin, *guttur,* throat. The common German name is *Kropf.*

The disease is probably prehistoric. It has been known for many centuries as a local endemic. As a familiar sight in the Alps it is alluded to by Juvenal (Sat. 13, 162):

> "Quis tumidum guttur miratur in Alpibus? . . .
> Nempe quod haec illis natura est omnibus una."

Pliny in the *Natural History* (Book XI, 68) remarks: "Guttur homini tantum et suibus intumescit, aquarum quae potantur plerumque vitio." ("The throat gets swollen [goitre] only in men and swine, mostly by reason of a poison in the waters drunk.")

Definition.—Simple goitre is primarily a *visible enlargement of the thyroid due to hyperplasia and vascular congestion.* In earlier stages it may involve no particular damage to the function of the gland, and even after the enlargement has increased in size and has existed for years, thyroid function may be fairly maintained. It is, however, often the first step toward almost any other disease (cysts, Graves's disease, tumors of all kinds, benign and malignant, cretinism, myxedema) with which the thyroid is ever associated.

Etiology.—*Geographical and Seasonal Range.* Hirsch[1] gives a long and exhaustive account of the distribution of goitre over the known world. His North American data may have been authentic for another century, but are long ago out of date and can now be read only with a smile. Pittsburgh, Pa., and Morgantown, W. Va., for example, he mentions as "endemic centers." This illustrates the fact that "endemic centers" appear and disappear. Historic continuity of the condition in one locality is not assured, though this has not cooled the interest and excitement of innumerable statisticians. Robert McCarrison[2] reports that in the Himalayas the disease varies widely even in adjacent villages, that its incidence fluctuates from year to year, that it appears in new villages and disappears from old ones.

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[1] Handbook of Geographical and Historical Pathology; Translated into English for the Sydenham Society, London, 1885, vol. 2.

[2] Etiology of Endemic Goitre, London, J. Bale, Sons and Danielson, 1913.

There is also a seasonal prevalence, and occasional plagues of epidemic goitre are described.

To quote further from McCarrison's interesting account: "Few countries appear to be entirely free from it. The disease is common in parts of England and Scotland. . . . Baillarger[1] estimated that in France alone, in 1873, there were no less than 500,000 goitrous individuals and 122,776 cretins. In Switzerland, between 1875 and 1887, over 12,000 young men were exempted from military service on account of goitre. . . . In Piedment, Lombardy and Venice, in 1883, there were 140,000 goitrous individuals among a population of 9,500,000. In some of the villages of the Himalayas, where my own researches have been carried out, it is difficult to find a man, woman or child not suffering from the deformity."

McCarrison further observes that while mountainous regions in the temperate and subtropical zones are more apt to be goitrous localities, the "disease is found at all heights above sea level where man can cultivate the soil." It is met with at a height of 10,000 feet, and again in the Delta of the Ganges, on the coast of Ceylon, on the coast near Manila Bay and in the Island of Arran off the coast of Scotland.

In the New World it is well known in South America.[2] For the United States and Canada, O. P. Kimball[3] gives some useful recent data. A wide goitre belt surrounds the Great Lakes and another is found in Oregon, Washington and British Columbia, on the slopes of the Cascade Range. Goitre is found in Ontario, in the valley of the lower St. Lawrence and in the glacial valleys of Alaska.

In North America the condition is relatively mild, but in many regions of the world goitre is a veritable scourge, and many newborn infants—often the offspring of goitrous mothers—suffer from all the forms of physical degeneracy and mental hebetude included in the term cretinism.

Race and Social Status.—No race is exempt. There is a family tendency to goitre, in that goitrous mothers are apt to bear goitrous offspring. In England cases have been observed to occur among the laboring and mining classes more frequently. The European peasantry are more frequent sufferers than the other classes. McCarrison found that in Gilgit and Chitral the incidence of the disease was much greater in those who worked for their living upon the soil.

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[1] Loc. cit., p. 59.

[2] Baillarger: Loc. cit.

[3] Crile and Associates: The Thyroid Gland, Philadelphia, Saunders, 1922.

Sex and Age.—Goitre occurs in sucklings, children, adolescents of both sexes, in child-bearing women and to a less degree in older men and women. The disease, on the whole, is considerably more frequent in women than in men. But this distinction is much more marked in some endemic regions than in others. French authors have not noted much difference, but in the Great Lakes goitre belt more than 80 per cent of all cases are in women, especially adolescent girls and pregnant and child-bearing women.

Metabolic Overstrain.—In the Atlantic States of this country, where goitre occurs almost entirely in young women and growing girls, it seems that metabolic overstrain must be credited for part of the trouble. Clinical inquiry will usually elicit more than one of the following facts: That the girl has been growing very fast, has recently begun to menstruate, has been eating enormously, participating in various athletic events at high school, dancing at night and going to bed at 1.00 A.M. A long car-ride to and from school, during which she perhaps has tried to study by a bad and vibrating light, has added to the strain.

After the seventeenth year, when girls have stopped growing, overstrain is still possible in various other ways. One patient of mine, a light-hearted girl from a southern city, who had lived comfortably with beaux, candy and dances for all her excitements up to her twenty-second year, came to New York and became a pupil nurse in a large New York hospital. Here she rose at 6.00 A.M., was on her feet all day, worked hard, studied at odd times and got to bed at midnight. Just two months of this life was followed by prompt appearance of the characteristic thyroid swelling. With correction of her regimen and diet and small doses of thyroid gland the swelling disappeared in about the same time it had taken to appear.

Goitre in Animals.—D. Marine[1] reported goitre in the dogs of Cleveland. The same student found it prevalent in sheep in Michigan. Marine and Lenhart[2] were able to show (Fig. 18) that in artificially bred trout the supposed thyroid "carcinoma" was only "a severe endemic goitre." Goitre has been noted in other animals, but more rarely. Baillarger[3] reported goitre as common in horses and dogs in France and very common in mules.

Water as a Cause of Goitre.—The literature of this part of the subject is enormous. The view of Pliny, the Latin naturalist

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[1] Cleveland Med. Jour., 1907, **6**, 45.

[2] Jour. Exp. Med., 1910, **12**, 311.

[3] Le goître et le cretinisme, Paris, Baillière, 1873.

(p. 57), was probably an echo of contemporary opinion. It has been claimed in Switzerland and France that certain natural springs are "goitrigenous," and there are on record many hundreds of analyses of supposed goitre-producing waters, the element at fault being variously said to be lime, magnesium, iron, copper, or even a "colloid poison."[1] Snow water from melting glaciers was for a long time believed to be the principal source of the "poison." Baillarger[2] concluded that goitre is "not exclusively found on any particular soil," a conclusion with which McCarrison agrees.

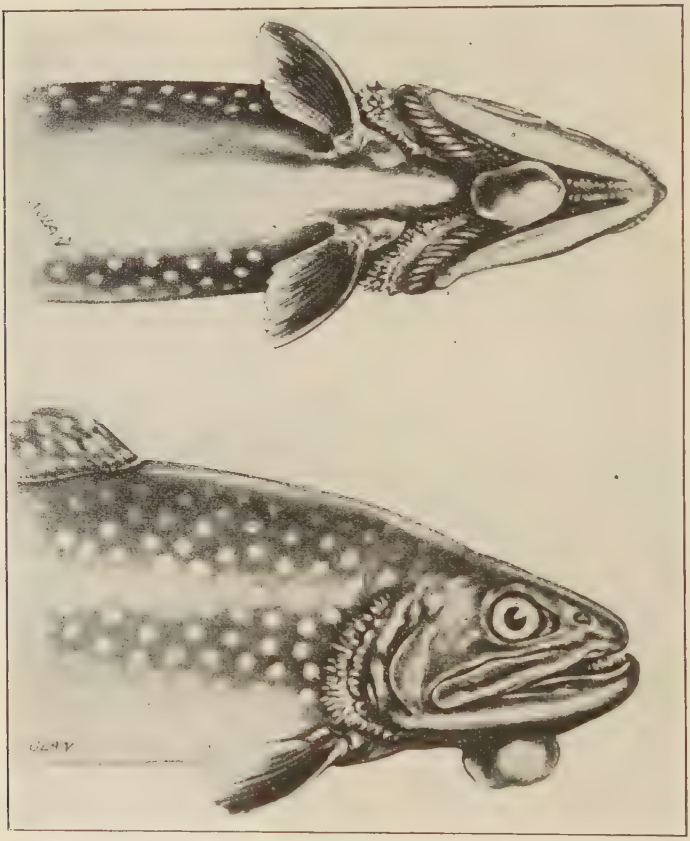

FIG. 18.—Location, size and relations of external visible goitre in brook trout. (Marine and Lenhart.)

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[1] Bircher: Kropfaetiologie, etc., Ztschr. f. exper. Path. u. Therap., 1911, **9**, 1.
[2] Loc. cit.

Essential Cause.—It is unnecessary to go any further into the etiology of goitre except to say that the essential cause has not been found. McCarrison[1] believed the cause of the disease to be a *contagium vivum* conveyed by water. He claimed to have produced a goitrous swelling in men by injecting the residues filtered from the water of goitrous districts, but he was not able to isolate any particular germ. Writing later, McCarrison[2] still holds that "There must be factors determining the production of goitre which are capable of exerting their effect even though the intake of iodine be adequate for all normal needs." He thinks that gastrointestinal infection is the chief of such factors, but that there may be many others now unknown. F. J. Shepherd[3] compares it to water-borne typhoid. Marine and Kimball[4] express the opinion that the ultimate cause of goitre is still unknown, but that the immediate cause is deficiency of iodine in the food and drink. This point is amplified under the paragraphs relating to preventive treatment (p. 63).

Pathological Anatomy.—The earliest noticeable enlargement may be diffuse, or smoothly nodular. The circumference of the neck may be increased several centimeters. Besides increased vascularity and thickening of the parenchyma there is a diminution in colloid and in iodine content. In later and neglected stages cysts, fibrocystic masses and adenomata may appear. These adenomata are believed (Marine and others) to develop from fetal cell rests. When actual tumor masses have developed they never, as a rule, entirely disappear, but the earlier swellings under treatment often subside, and sometimes even without treatment disappear.

Symptoms.—There is no pain at first. The beginnings of enlargement are often first noticed by the patient's relatives or friends. The tumor may appear in a few weeks' time, remain stationary for weeks or months or years, grow larger, grow smaller, disappear, or (more often) develop into a much more serious and permanent complication Graves's disease, chronic hypothyroidism, myxedema or malignancy. Occurring congenitally, goitre usually issues in cretinism. On the other hand, in both acute and chronic stages, the patient may get on comfortably for years without marked secretory derangement of any sort.

Mixed tumor masses starting in this way may assume enormous size (as big as a child's head and bigger) with passing time, and become dangerous from pressure on vital organs—the recurrent laryngeal nerve, vagus nerve, cervical veins, gullet, windpipe. Death from asphyxiation is not uncommon; hoarseness, headache and dysphagia are also noticed. Some goitres have attained such size and curious shape as to have been recorded among the anomalies and curiosities of medicine. J. L. Alibert[1] mentions cases where the goitre was pendulous, hanging over the breast or even to the middle of the thigh. Yet it must be also noted that many large goitres interfere but little with health and efficiency. I have known one middle-aged woman with an immense struma who ran a private hospital successfully for many years. Another was a very competent matron of a boy's boarding school. In communities where endemic goitre is prevalent virtually all the business and manual labor of the township is done by people with goitres.

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[1] The Thyroid Gland, London, Baillière, Tyndall and Cox, 1917.

[2] Brit. Med. Jour., 1924, **1,** 989.

[3] Report of Commission of Conservation of Canada, December, 1919.

[4] Jour. Am. Med. Assn., October 1, 1921.

Diagnosis.—The diagnosis must be based upon the history, the local signs and the absence of complicating secretory troubles. A metabolism determination will often be helpful. In short thick necks a roentgen-ray photograph will often give a good picture of a thyroid gland.

Prognosis.—This may be inferred from the general description of the disease already given. In acquired goitre seen in its earliest stages and promptly treated the prognosis is good. In congenital goitre occurring in an infant with a goitrous mother the chances of cure are small. Cretinism is the usual outcome. Some patients with mild acquired goitre recover spontaneously.

Treatment.—*Hygienic.*—The patient's diet and mode of life should be carefully reviewed. Causes of metabolic overstrain should be removed. Rest must be insisted upon. Bad teeth, swollen tonsils and constipation must be properly cared for. The presence of pus in the urine must be looked for, and in females gonorrheal vaginitis must not be forgotten.

Curative.—Intestinal antisepsis is always useful. McCarrison[2] cited numerous cases of benefit and apparent cure from thymol and *Bacillus acidophilus* milk. Almost ever since its discovery by Gay-Lussac, in 1813, iodine in various forms (Lugol's solution, potassium iodide) has been known to be of some benefit. Thyroid extract (see Thyroid Therapeutics, page 110) in very small and frequently repeated doses may be helpful in early cases. This treatment is, however, an edged tool, and in careless hands may result in conversion of a small benign goitre into a case of Graves's disease.

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[1] Encyclopædia Brittanica; 11th ed., Goitre.

[2] Loc. cit.

When tumor and cyst formation have ensued, or secretory disorders have arisen, the treatment must be that suitable to the individual case. The surgical relief of goitre is to-day an immense subject, thoroughly dealt with in the surgical text-books. The care of disordered secretion is discussed in subsequent sections of this chapter.

Preventive.—The researches of D. Marine and co-workers[1] have raised the hope that preventive treatment with minute doses of iodine will perhaps eventually root out the disease as an endemic scourge.

Marine's statement that the immediate cause of goitre is lack of iodine can hardly be reaffirmed any more than it can be claimed that the immediate cause of malaria is lack of quinine. But there seems no longer any question that the prolonged administration of infinitesimal doses of iodine (sodium iodide) to all the susceptible population of a mildly goitrous district, such as that of Ohio, will virtually prevent the appearance of the disease during the period of treatment.

Marine and Kimball[2] give the following interesting description of their methods and results:

"Working with endemic goitre in brook trout in 1909 and 1910, Marine and Lenhart were able to demonstrate that iodine added to the water in a concentration not exceeding 1 to 1,000,000 arrested or prevented the development of thyroid hyperplasia (goitre). Since then the method has been successfully applied on a large scale by several observers in the prevention of goitre in cattle, sheep, pigs and poultry.

"To our knowledge the prevention of human goitre was not attempted on any large or practical scale until 1917, when we began work with the school population of Akron, Ohio, although in Cleveland it had been strongly urged, and had been used by some physicians for several years. Briefly, the method as applied to man consisted in the administration of 2 gm. of sodium iodide in 0.2 gm. doses distributed over a period of two weeks, and repeated each autumn and spring. This amount of iodine is excessive. . . One gram over a longer period would be better. The important thing is that iodine for thyroid effects should be given in exceedingly small amounts, and it is believed that most of the untoward effects recorded are due to the excessive doses employed.

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[1] Jour. Am. Med. Assn., 1921, **77**, 1068.

[2] Loc. cit.

"The results of our two and a half years' work on school girls at Akron are as follows: Of 2190 pupils taking the dose above mentioned only 5 have developed enlargement of the thyroid; while of 2305 pupils not taking the prophylactic 495 have developed the thyroid enlargement. Of 1182 girls with thyroid enlargement at the first examination who took the prophylactic, 773 thyroids have decreased in size; while of 1048 pupils with thyroid enlargement at the first examination who did not take the prophylactic, 145 thyroids have decreased in size. Klinger (1921) has reported even more strikingly curative results in the school children of the Zürich district."

These authors also emphasize the value of the treatment for pregnant women, as not only the mother but the offspring is thereby protected. The same dose (2 gm. of sodium iodide or its equivalent in any other form of iodine) is to be distributed over the first half of the period of pregnancy.

Unfavorable complications were "conspicuous by their absence." No untoward effect was noted save iodism in 11 instances, mostly so mild that the girls did not stop the treatment.

Marine and Kimball further suggest that the above procedure should be a standard practice for adolescents in goitre regions. "Beginning with the period of puberty goitre occurs about six times as often in girls as boys. The question therefore whether general prophylaxis should include both boys and girls would depend on whether the particular district was mildly or severely goitrous. . . . In the United States probably the maximum of prevention with the minimum of effort would be obtained by giving iodine between the ages of eleven and seventeen years.

"The prevention of goitre means vastly more than the elimination of cervical deformities. It means in addition the prevention of those forms of physical and mental degeneration, such as cretinism, mutism and idiocy, which are dependent on thyroid insufficiency. Further it would prevent the development of thyroid adenomas, which are an integral and essential part of endemic goitre in man and due to the same stimulus. These growths once initiated are frequently not controlled by iodine, as are simple hyperplasias. The terminal metamorphoses are far more serious; probably 90 per cent of the malignant tumors of the thyroid arise from these adenomas.

"If the prevention of goitre is good preventive medicine it is still better preventive surgery. With so simple a means of prevention at our command, this human scourge can and should be controlled, if not eliminated."

R. McCarrison's dissent from this view is noted above, p. 61.

2. GRAVES'S DISEASE.

Synonyms.—These are numerous. Owing to the less universal interchange of medical literature in former years, the disease has been independently recognized at different times by various observant physicians. Flajani is said to have described it in 1800; Parry, in 1815; Basedow, of Merseburg, wrote fully of the three classical symptoms in 1840. The English physician, R. J. Graves,[1] also described it independently. National partiality has influenced the prevalence of personal designations. *Exophthalmic goitre, hyperthyroidism* and *hyperthyreosis* are other terms. Possibly exophthalmic goitre is the most popular term in America. Names inferring more about the etiology of the disease than is positively known should be avoided in this connection and used elsewhere only in their physiological sense.

Definition.—A working definition of Graves's disease, not involving the affirmation of disputed and unknown points in the pathogeny of the disease is hard to give. Perhaps William Osler's statement is as good as any: "A disease characterized by exophthalmos, enlargement of the thyroid and functional excitement of the vascular system." Exceptions and objections to this definition will be evident as the reader gets on in the subject.

Predisposing Causes.—*Prevalence and Distribution.*—The disease is known all over the world. It is more common in those regions of this country where endemic goitre exists. But it may appear anywhere. McCarrison[2] found it rare in the regions of India where goitre is endemic, but American experience seems to be duplicated in most parts of France and Switzerland.

Age.—The disease is rare in children. Holt and Howland[3] say it is unknown under five years of age. Of 3477 cases collected by Sattler[4] only 184 were in children under fifteen years of age. After the forty-fifth year it is rarer, but not unknown by any means, and the cases, when occurring, are often severe.

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[1] Clinical Lectures, Philadelphia, Waldie, 1838; reprinted from an English journal of 1835, which is not to be found in the Library of the New York Academy of Medicine. Ordinary text-book references are incorrect, and have been copied from book to book without verification.

[2] Loc. cit.

[3] Diseases of Infancy and Childhood, Appleton, New York, 1923.

[4] Quoted by McCarrison: Loc. cit., reference to original not given.

Social Condition.—Examination of statistics shows that there is no very well-marked social cleavage in the distribution of the disease. Heredity and predisposition are not more evident than in other diseases of the thyroid.

Sex.—An immense majority of the cases is found in women. All observers are agreed on this point. Figures gathered from a variety of sources show an incidence of about 9 in women to 1 in men. The disease is much more prevalent in young women, that is, in women from fifteen to forty-five or fifty years of age, the period of sexual activity. One is therefore justified in supposing that the menstrual nisus, pregnancy and lactation are related to the disease, but whether by reason of some specific relation of the female sex hormones to the thyroid, or only as a matter of physical overtaxation, cannot be scientifically affirmed (see Chapter XIII).

Hygiene.—Unfavorable and depressing surroundings—bad food, improper housing, overwork—are not to be forgotten as predisposing causes, but they cannot be said to have any special influence upon the development of this particular disease. They only reënforce other causes.

Other Diseases.—Great stress is laid by a number of writers upon *disorders and diseases of the alimentary tract.* Not only constipation, but chronic appendicitis, adhesions of the bowels, gall stones, ulcer, dilatation, kinks, diarrhea, intestinal putrefaction, worms, are enumerated. By some writers the recovery of a case of Graves's disease after an operation for chronic appendicitis is thought *prima facie* evidence of the causal relation. But there are other possibilities: The curative effect of operation *per se,* the resulting benefit to the patient's general health, with stimulus to the *vis medicatrix naturæ,* the possibility that the patient would have recovered anyway, are all reasonable assumptions. Nobody should try to work out the causal relations of this disease until he has mastered the story in J. S. Mill's *Inductive Logic* of: (1) The method of agreement, (2) the method of difference, and (3) the method of concomitant variations.

Frequently associated with Graves's disease is the history of some recent infectious disease. *Influenza* is such a common antecedent as to justify the suspicion that the relation is significant. Among other antecedent infections are typhoid, acute tonsillitis, rheumatic fever and secondary or hereditary syphilis. To these, of course, must be added chronic tonsillitis, pyorrhea, alveolar abscess and septic infections of the urinary bladder, renal pelvis or middle ear. We have, however, no scientific ground for believing that these conditions do more than render the patient more susceptible to the incidence of the disease.

Psychic Antecedents.—Many patients with exophthalmic goitre date their trouble from a shock or strain. The sudden death of a relative, a fright, a railway or automobile accident, a military invasion in war; or less acutely a long watch by a sick bed, or an accumulation of business anxieties, may be the thing the patient tells you of first.

It is a curious fact that the typical facial expression of Graves's disease is that of panic fear; the wide, protruding eyes and horrified expression, the fast-beating heart, the sweating and tremor are the usual autonomic reflexes of fear. This remarkable coincidence has led many to suppose that Graves's disease is essentially a disease due to chronic stimulation of the sympathetic nervous system. This is, however, another argument which has an undistributed middle in its premises.

Morbid Anatomy.—The *post mortem* findings often give little notion of the chemical tumult which attends severe cases of the disease.

Eyes.—The eyes often protrude after death. The cause of this has aroused much curiosity, but so far as I am informed nothing has ever been found except a possible increase of the retrobulbar fat. I once made serial sections of the orbital tissue of such a case. Careful examination of many, stained in a variety of ways showed nothing unusual. All the vessels were collapsed. It might be maintained that early *rigor mortis* of the orbital muscles retains the bulbus in the *ante mortem* position. But this is a hypothesis not sustained by the fact that in recovered cases the exophthalmos often persists for years.

Heart.—The heart is often found unaffected by anything not connected with overwork. In advanced cases there is hypertrophy of the left ventricle, with crumpling and insufficiency of the valves—permanent conditions which do not entirely disappear, though the general condition of the patient may have much improved. Preexisting valvular disease is aggravated. Acutely fatal cases show myocardial degeneration with foci of lymphocytes among the muscle fibers.

Thyroid Gland.—Not all cases of Graves's disease are associated with enlargement of the thyroid. In Murray's statistics the thyroid was found to be small in 4.3 per cent of the cases. When the thyroid enlarges the macroscopical appearances vary. Usually the gland is diffusely swollen; lobes and isthmus are soft to the touch, and congested. One lobe may, however, alone be involved, or be much larger than the other. Graves's disease sometimes comes in patients who have already for many years had a simple goitre. In these instances the configuration and consistence are that of the cystic, fibrocystic, fibrous or adenomatoid condition previously present.

The speed of enlargement varies. It sometimes comes on in a few days or even hours—a soft, fluctuating swelling as a rule—with a fulminating general toxic condition often rapidly fatal. Physicians of large experience in this disease have usually seen several such cases in the course of twenty or twenty-five years' practice.

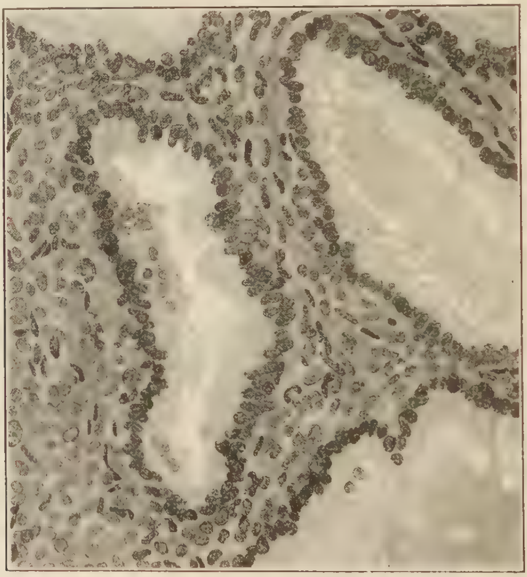

FIG. 19.—Advanced stage of thyrotoxic cellular hyperplasia. Note reduplication of alveolar cells. × 360. (Crotti.)

Under the microscope there is hyperplasia of the epithelium (which becomes tall, cylindrical and makes papillary projections into the lumina of the gland), diminution of colloid, engorgement of the vessels (Fig. 19). This microscopical picture appears to have been first noticed by W. S. Greenfield,[1] and was extensively confirmed in the next few years.[2] I reported a microscopical analysis of several cases.[3] J. Ewing[4] made an elaborate pathological study of the condition, with many well-drawn plates. Greenfield called it "a gland in evolution," the high cylindrical and papillated epithelium, increased number of alveoli and diminished colloid seeming to sustain this view. But S. P. Beebe[1] called attention to the fact that the thyroid in Graves's disease contains less iodine than the resting, *i. e.*, normal gland. D. Marine has confirmed Beebe's observation. Lenhart, MacCallum and Goetsch have advanced the view that the Graves hyperplasia starts in localized fetal adenomata, and may remain confined to these parts of the gland. L. F. Barker has suggested that the hyperplastic process may be absent in the thyroid proper but present in an accessory thyroid, most often an intrathoracic goitre.

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[1] Brit. Med. Jour., 1893, ii, 1260; Lancet, 1893, ii, 1495.

[2] For bibliography, see P. H. Moebius, Basedow'sche Krankheit, Nothnagel's spec. Path. u. Therap., vol. **22**.

[3] Presbyterian Hosp. Repts., New York, 1898.

[4] Ewing, J.: New York Med. Jour., 1906, **84**, 1061.

It has been claimed that even in those cases where the thyroid remains small, microscopical study of sections will always show small and scattered adenomatoid patches. This contention is especially eager with those who insist that the thyroid dyscrasia is the first link in the chain of causes which produces the disease. But the coincidence of such phenomena, even when constant, does not relate them as cause and effect; they may be also effects of a common cause, which is to be sought elsewhere.

In the later stages of the disease the gross and fine structure is variable. After early cure there may be a *restitutio ad integrum* more or less. When myxedema supervenes degenerative and atrophic changes in the epithelium are evident (see Myxedema, p. 102), though the mass may be still hard, nodular and bulky.

Thymus Gland.—The thymus gland is sometimes much enlarged in Graves's disease. I have seen it at autopsy as large as a man's hand, and covering the whole front of the pericardium. The reasons for this occasional enlargement are very obscure. Further comment will be found in Chapter XI. The speculations of W. S. Halsted[2] were interesting but inconclusive. By Blackford and Freligh[3] a study was made of the thymus in 100 fatal cases of Graves's disease in the hope of finding some relation between that disease and the size of the thymus. They reported the gland hypertrophic in all cases under forty and one-half the cases over forty years of age. They make the following critical comment: "Our records show that the most severe and acute cardiac damage is seen in the violent intoxications beginning after the age of forty, that is, in the 'menopause' group. These, as a rule, have a small thymus or no thymus. . . . The findings indicate that a thymic hypertrophy and lymphatic hyperplasia should be considered as a result rather than as a cause of the . . . goitre. Hypertrophy of the thymus probably depends on toxic stimulation of vestiges present at the onset of the disease."

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[1] N. Y. Med. Jour., 1911, **94**, 73. [2] Bull. Johns Hopkins Hosp., 1914, **25**, 223.

[3] Collected Papers of The Mayo Clinic, 1916, **8**, 507.

The microscopical appearances of such cases as I have seen were negative. That is, there was a simple hyperplasia. The thymus does not appear to enlarge enough to cause any pressure symptoms. G. W. Crile[1] remarks: "In our experience we have never had a single case of hyperthyroidism in which we had reason to consider an enlarged thymus a complicating factor."

Lymph Nodes.—Lymphatic enlargement is commonly reported. It may affect all the chains of lymph nodes in the body. Lymphoid tissue in the thyroid itself and in the bone-marrow (Marine) is also said to be increased.

Blood.—The Cells. There is a relative lymphocytosis with a decrease in the polymorphonuclears. Anemia is not a special sign of Graves's disease, though it may be present. The blood clots slowly; a few cubic centimeters for a Wassermann test may remain fluid for hours after withdrawal. None of these conditions is especially characteristic. Marine and Lenhart have suggested that a marked lymphoid hyperplasia may be a useful indication of the severity of the disease.

The percentage of *blood sugar* is often increased. The possible relation of this fact to an influence exercised by the thyroid secretion on the pancreatic sugar function will be discussed in Chapter XIII. The blood sugar rises to 0.13, 0.14 per cent and higher. When the "renal threshold" is passed glycosuria appears. This glycosuria must be distinguished from those cases in which diabetes was already present before hyperthyroidism developed.

Serology.—The writer, with the assistance of J. Koopman, has worked out certain serological facts in respect of the blood in Graves's disease which are of some interest in their bearing on the pathology of the condition. The confirmatory work of Terry and Shepardson[2] is the more interesting, as they do not seem to have noticed our previous studies. There appear to be no other accounts of serum fixation tests in thyroid disease except a series of observations by A. Papazolu,[3] made in conjunction with Professor Marinesco. Their use of alcoholic antigens appears to have confused their results with luetic fixations. Mr. Koopman has kindly prepared for me the following summary[4] of the test:

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[1] Loc. cit., p. 58.

[2] Jour. Am. Med. Assn., 1923, **81**, 1435.

[3] Séances et mém. soc. d. biol., 1911, **71**, 671.

[4] Med. Record, January 28, 1922. My sincere thanks are due to the Publishers of the New York Medical Journal and Record for permission to use this account again.

"The blood of some patients who show symptoms of Basedow's disease binds complement in the presence of an antigen made from normal thyroid glands of dogs or guinea-pigs.

"The reaction may be due to a specific thyroid substance which combines with an antibody in the blood of the patient.

"The best method of preparing the antigen which we have been able to find is as follows: The glands are obtained under aseptic precautions as soon as possible after the animals have been killed. Each gland is trimmed carefully and minced finely with sterile scissors. The whole mass is then ground in a mortar with a convenient quantity of washed and sterilized sand and of dry sodium chloride. The amount of sand is of no importance, but the salt should be added in the proportion of $\frac{1}{10}$ gm. to each gram of gland used; a few drops of 2 per cent aqueous solution of tricresol are added for each 10 gm. of thyroid. This mixture is bottled and laid away in the ice-box. For use it is made up with distilled water, using 10 cc. of water to 1 gm. of the original amount of gland. The sand and solid matter are removed with the aid of a centrifuge.

"It is best (but not absolutely essential) to use the mixed glands of five or six dogs (or guinea-pigs). As at present prepared, the extract contains much extraneous matter which takes no part in the reaction; if some method of securing the antigenic substance free from all foreign matter could be devised the specificity would be enhanced. As far as we have gone, we know that the antigen slowly deteriorates, even when kept under the best conditions, and after about three weeks it is necessary to obtain a new supply. Drying instantly spoils its antigenic properties and it does not withstand heating to 50° C. for fifteen minutes.

"The test is set up in the form of a titration, using a constant amount of serum which is not more than one-quarter of the least amount which is anticomplementary. The antigen is used in varied amounts, beginning with an excess and ending with the least amount which can be expected to give fixation. The exact amounts used will depend upon the total volume of the test the worker is accustomed to using. At the same time an antigen control is made with the same quantities of antigen as are put in the test. This procedure will obviate the necessity of putting in a separate titration of the antigen before the test itself is made. The result is indicated by the difference between the quantity of antigen which is anticomplementary of itself and the quantity which binds complement in the presence of serum. A negative serum with the antigen will often bind less complement than the antigen alone.

"A serum is considered positive when it binds complement in in the presence of one-half or less than one-half of the anticomplementary dose of antigen, and the smaller the amount of antigen necessary for complete fixation the stronger is the reaction. Fixation is carried out for from four to six hours in the ice-box. At the present time the range is short, but with improved methods of preparing the antigen it is hoped the range will become greater.

"Besides tests on human glands and human tumors (*i. e.*, thyroid tumors), we have tried the glands of some other animals, namely, guinea-pig, bullock and pig, and we find that only guinea-pig glands give results comparable with the dog antigen.

"Much more work remains to be done on fixation results with extracts of true exophthalmic goitres. These are now very hard to get in New York operating rooms, as surgical removal of them has gone out of fashion, and when gotten we have not been able to devise any way of keeping them in fit condition for antigen formation for more than two or three weeks."

In the section on Diagnosis some further comments will be found on the practical application of this test.

Abderhalden's reaction (*Schutzferment*) has not attracted much attention in thyroid serology. It also is mentioned again under Diagnosis.

Nervous System.—Definite pathological changes have not been found in the brain and cord. L. B. Wilson[1] found changes in the sympathetic ganglia of the neck. The precise relations of these findings to hyperthyroidism are uncertain. The profound excitement of the sympathetic system, as far as present evidence goes, is "functional," that is, the chemical changes are not accessible to microscopical study.

Etiology.—The cause of scabies is the itch mite. The etiology of malaria is scientifically explained by the curious story of the Plasmodium malariæ and Anopheline mosquitoes. Myxedema may be symptomatically explained as due to extreme deficiency of the thyroid secretion. But in the case of the Graves syndrome no such prompt and comprehensive answer can be now given. The question is *sub judice.* The data are insufficient for a scientific conclusion. To review even briefly the mountainous mass of inconclusive literature on the subject would serve no very immediate practical purpose, and nothing more will be attempted here than a short notice of the more popular hypotheses.

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[1] Am. Jour. Med. Sci., 1916, **152**, 799.

The *toxic theory* has its advocates. McCarrison[1] in the case of simple goitre has made a strong plea for the selective affinity of certain toxins (presumably of bacterial origin) for the thyroid. He suggests the same mechanism (bacterial invasion or toxemia) as the ultimate and essential cause of the varied symptoms of Graves's disease, the crippled thyroid secondarily producing the signs not otherwise explained.

The *neurogenic theory* is based upon the *post mortem* findings in the brain, medulla and sympathetic ganglia. But not only the findings are uncertain; the interpretation of the findings is equally difficult.

The *thyrogenic theory*, that Graves's disease is a clinical type of primary hyperthyroidism, is that most generally held. It is based upon the increased size of the gland, and the fact that many of the signs of the Graves syndrome may be produced in the normal subject, particularly the tachycardia, the tremor, and the increased metabolism by administering thyroid to normal men and animals in excessive doses. But exophthalmos cannot be produced in this way, and some cases of Graves's disease are not accompanied by enlargement of the thyroid. Those insisting most strongly on the thyrogenic theory are driven to the supposition that even a small thyroid may contain adenomatoid patches functioning excessively; but there is good surgical evidence that in the case of small thyroids partial excision does not cure the disease. After the psychic effect of such an operation has passed the patients are apt to be worse than before. Moreover the supposition that not merely an excessive but a *perverted* or *toxic* thyroid secretion is liberated by the thyroid in exophthalmic goitre, while it has some justification in the clinical course and symptoms of many cases, still fails as an explanation when the thyroid is small. In fine, the primary underlying cause of Graves's disease is at present unknown.

G. W. Crile[2] has described Graves's disease as "Not a disease of a single organ, or the result of some fleeting cause, but a disease of the motor mechanism in man . . . establishing a pathological interaction between the brain and the thyroid. . . This interaction may be broken by diminishing the thyroid output (operation) or by securing physiological rest." This statement C. P. Howard[3] characterizes as being "romantic," and it is difficult to classify it in any other way.

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[1] Loc. cit.

[2] Am. Jour. Med. Sci., 1913, **145**, 28.

[3] Barker's System, vol. **1**.

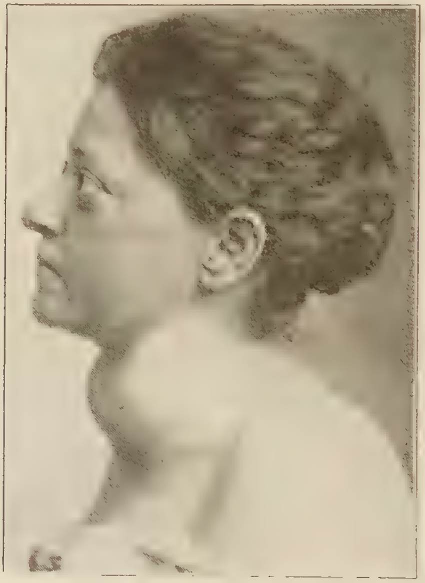

FIG. 20.—Exophthalmic goitre. (Hammond.)

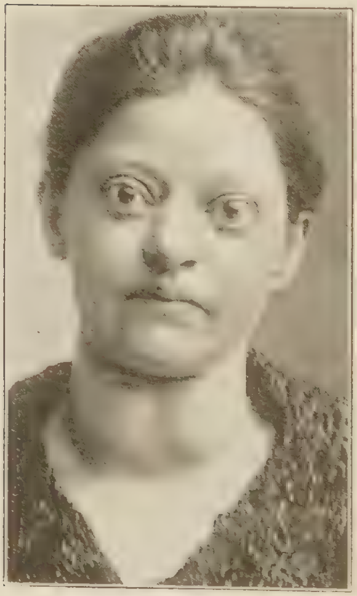

FIG. 21.—Exophthalmic goitre. (Hammond.)

The presence of thyroid antibodies in the blood in Graves's disease (p. 70) has, it seems to me, a significant bearing on the etiology; but there are no data sufficient to settle the matter at the present time.

Symptoms and Signs.—In the section just previous many of these have been already incidentally mentioned.

Eyes.—A protrusion of the bulbus oculi (Figs. 20 and 21) is an early and characteristic sign of the disease (*Glotzauge* of Basedow) appearing in about three-fourths, or one-half, or one-third, of various reported series of the cases. It is called *exophthalmos* (Greek, ἐξ, and ὀφθαλμός, eye). Probably no subject in clinical medicine has been more thoroughly threshed over than this. Medical undergraduates have sighed these many years over the fruitless multiplication of minutiæ, each with a physician's name attached. To mention only a few, we have: Stellwag's sign, infrequent winking; von Graefe's sign, failure of the upper lid to follow the ball when the patient looks down; Moebius's sign, deficient axial convergence of the eye-balls on close objects; Dalrymple's sign, widening of the palpebral fissures. All these small matters, while amusing, mostly depend at last on the simple mechanics of protrusion. But one must note in addition that the protrusion in Graves's disease is *elastic.* When one has determined the presence of an *elastic exophthalmos,* one has done all that is necessary. In border-line cases it is not, however, always easy to decide the question. Haig's rule I have found of value, namely, that the closed lid in health at the level of the cornea clears but does not encroach on a straight-edge ruler (or other convenient clean straight object—glass tube, wooden tongue depressor) laid across the orbit from the brow to the malar prominence. This is a good general rule, showing occasional individual and perhaps racial exceptions, but reliable in a great majority of instances. If the patient knows nothing of her eyes, the desired information, whether they have recently become more prominent, can often be obtained from family or friends.

The exophthalmos of Graves's disease must be carefully distinguished from the long eye-ball of myopia, the prominent eyes of the chronic asthmatic, the mechanical protrusion due to chloroma (which is sometimes bilateral) and other tumors, and to retrobulbar abscess and hemorrhage.

Unilateral protrusion is rare but not unknown. Unequal protrusion on the two sides may be noticed. The scleræ are often glistening and shiny. The pupils are sometimes a little unequal, but this may be also due to refractive differences between the two eyes long antedating the onset of the exophthalmos. Lacrymation may be present. The lids may be edematous and pigmented. There may be a fine tremor of the lid muscles. In late stages paralyses of various external muscles have been noticed; optic atrophy has occasionally been reported. The retinal artery may pulsate, and a bruit is sometimes heard by placing the stethoscope on the eye-ball.

The degree of protrusion varies with the nervous condition of the patient; it is said to be more marked when the patient is especially excited, or when the blood-pressure is unusually high. Even in sleep the lids may not be completely closed.

Efforts have been made to explain the exophthalmos as resulting from a persistent spasm of the levator palpebrarum, or of the protrusor bulbi (muscle of Müller). The latter muscle is unstriated, and is believed to be innervated by the sympathetic. Whatever the cause, the effect often outlasts the disease, remaining as a permanent disfigurement. As already noted, it may even persist *post mortem.*

The Thyroid Enlargement has been already partly described (p. 67). There is a greatly increased arterial vascularity, and often there is a systolic bruit noticeable with the stethoscope, and a visible and palpable pulsation in the soft, hot and tumefied gland.

Heart and Bloodvessels.—The heart beats fast. This is one of the earliest signs of the disease and perhaps the most constant; without tachycardia a diagnosis of a case seen for the first time cannot be made. The pulse-rate runs all the way from 90 to 200 per minute. The speed of cardiac action is abnormally increased by physical exercise, mental anxiety and intercurrent febrile disease. Hypertrophy and dilatation of the heart develop in time, and murmurs appear, at first due to relative insufficiency perhaps, but later on arising from true valvular trouble. The patient has also many subjective signs of distress in the region of the heart, and palpitation may be extreme. Prolonged rest in bed fails often to bring the pulse-rate lower than 100. Arrhythmias of various kinds are reported. The action of the heart may be violent enough to make the chest heave and the bed shake. Graves[1] has mentioned a case where he could hear the sounds of the heart 4 feet from the patient's body.

The *blood-pressure* is around normal figures in early stages; when the disease has lasted several years, blood-pressure may reach 150 or 160 mm. systolic, or more.

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[1] Loc. cit., p. 65.

Muscles.—One of the most constant and characteristic early signs of the disease is *fine tremor of the voluntary muscles.* The tremor is of slight excursion, 8 to 12 per second, exaggerated by mental excitement, almost never entirely absent in waking hours. It is best observed by having the patient extend the forearms and hands and spread the fingers. A sheet of stiff paper laid on the extended fingers trembles quite violently by transmitted impact. Muscular actions requiring exact coördination are difficult; general muscular weakness is present; exercise is fatiguing.

Nervous System.—Temperamental instability is characteristic. The patient is easily worried and frightened, cries readily, sleeps badly. More serious mental symptoms, melancholia, mania, hallucinations and delusions, suicidal and homicidal tendencies have been reported. Fortunately they are rare.

Skin.—Flushing and paling are common. Sweating is very common. Patches of redness due to localized capillary congestion are common. Sensations of heat and cold are complained of. When the action of the heart is very violent a capillary pulse resembling that classically noted in aortic regurgitation may be elicited by the proper technique.

Finally it is to be noted that *cutaneous pigmentation* is a significant sign of the disease. One may see large areas, patches or spots of pigmentation or a general browning of the skin. Leukoderma is likewise sometimes seen. Sometimes the pigmentation has been marked enough to suggest Addison's disease.

The condition of the *blood* has been discussed in the section on Morbid Anatomy.

Kidneys. These are only secondarily affected. Albuminuria is sometimes seen, but nephritis is not a part of the uncomplicated disease. Glycosuria has been mentioned on another page (p. 70). The percentage of sugar in the urine is small; often only traces are present. Some cases have no glycosuria at any time.

Digestive System.—The digestive system participates in the general commotion. Loss of appetite, increased hunger, preferences for special articles of food, constipation, diarrhea and vomiting are familiar manifestations of the digestive disorder. Malnutrition is the rule, and the patient may lose weight rather rapidly, even when eating a large amount of food.

Respiratory System.—The rate of breathing increases in proportion to the pulse-rate. Patients breathe irregularly, and even in sleep may have a very disturbed respiration. Paroxysms of dyspnea may occur, almost always nervous. Cough, aphonia, bronchitis, even a bronchorrhea, have been described. The last condition must certainly be secondary.

Temperature.—The body temperature in Graves's disease is elevated. The degree of fever is variable. Severe cases may run a temperature of several degrees. Elevations of 0.5° and 1° F. are common. The diurnal variation is as in health.

Basal Metabolism.—By reason of the fever, the hurried breathing, the rapid action of the heart and the continuous muscular tremor one would anticipate a rise in the metabolic rate, and the question has been settled affirmatively by a multitude of researches extending over many years back from the present time. In a large majority of cases of Graves's disease the metabolic rate rises 20, 30, 50 and even 100 per cent above normal. In Chapter III modern methods of metabolic study are briefly described and bibliographical sources indicated.

A conservative statement of calorimetric findings in Graves's disease by E. F. Du Bois[1] covers the ground well: "The measurement of the heat production gives us the best index of the severity of the disease and of the effects of treatment. Very severe cases show an increase of 75 per cent or more above the normal average; severe cases, 50 per cent or more; moderately severe and mild cases, less than 50 per cent; while a few mild and several atypical cases, or cases in which operation has been performed, may be within normal limits. In severe cases the warmth of the skin and the sweating can be accounted for entirely by the necessity for the increased elimination of heat.

"The specific dynamic action of protein and of glucose is within normal limits. . . . The methods of direct and indirect calorimetry agree very closely when one considers the technical difficulties. . . . The law of the conservation of energy holds good in exophthalmic goitre, and there is no profound disturbance of the intermediary metabolism."

The bearing of the basal metabolic rate on the diagnosis of the disease and the progress of treatment will be noted later in this chapter.

Sex Organs. It cannot be said that the sex organs in either man or woman suffer more than secondary changes during an attack of Graves's disease. In women, if the anemia is marked or nutrition is impaired, menstrual irregularities are to be expected. A search through the large literature of the subject rather produces the impression that many of the uterine and ovarian abnormalities described were not causally correlated with the thyroid trouble.

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[1] Arch. Int. Med., 1916, **17**, 915.

Acidosis.—It does not appear to me that the *acidosis* often described as a symptom of Graves's disease is more than an accidental concomitant.

Diagnosis.—The diagnosis of Graves's disease is one of the easiest and one of the most difficult problems in clinical medicine. In Germany the three "cardinal signs" (eyes, thyroid, heart) as described by Basedow are still called after Basedow's native city, the "Merseburger trius." The muscular tremor, the sweating and the cutaneous pigmentation are also diagnostic signs. When all these are found together, with a history of recent acute or subacute onset, the diagnosis is perfectly secure. But every one of these signs may be a source of deception.

Under Symptomatology it has been already noted that myopia, tumors of the orbit and chronic asthma also cause a protrusio bulbi, and that congenital and racial protrusion must be also allowed for. In some cases of Graves's disease exophthalmos does not occur.

In respect of the thyroid swelling likewise there may be troublesome doubts. The size of the gland often gives no indication of its function. Indeed, in a majority of strumæ of over two years' duration the enlargement is rather an indication of underfunction than of overfunction. Moreover some chronic benign and quiescent goitres may rather acutely take on a toxic function. Finally, the thyroid swelling may be absent. Delafield years ago used to tell his students that the diagnosis of exophthalmic goitre must sometimes be made without the exophthalmos and without the goitre.

Of the tachycardia it is also true that many causes besides Graves's disease are at times active. The extrasystolic storm commonly called *paroxysmal tachycardia* may be diagnosed by a cardiographic tracing, but the fast heart of failing compensation in valvular disease is often a puzzle; many toxic conditions, especially the abuse of tobacco, may present themselves; early tuberculosis, a bad tooth, a smouldering tonsillitis and other subacute bacterial infections speed up the heart. Occasionally one of more of these conditions may coëxist with Graves's disease.

As to tremor, tobacco tremor, alcoholic tremor, neuritic tremor, familial or hereditary tremor are also fine oscillations closely resembling the Graves tremor. All these possibilities must be carried in mind.

The slight elevation of temperature is often more of a hindrance than a help, for it suggests much more commonly a bacterial infection than a beginning thyroid trouble.

French writers attempted formerly to simplify the diagnosis by classifying all the doubtful cases as *formes frustes,* and calling them all "maladie Basedowienne." But many mistakes arise in this way; a diagnosis is not justifiable on such a meagre clinical basis.

Finally, after the lapse of years, in obstinate or improperly treated cases, though the heart continues irritable, the cystic and fibrous gland is still large, and the eyes have not receded, yet the patient has really become hypothyroid, and the diagnosis can hardly be made any longer by clinical signs alone.

Laboratory Helps, therefore, have become essential.

Among these may be mentioned, first, *increase in the rate of basal metabolism.* Details of the metabolism in Graves's disease have been already noted (p. 78). This sign is often of value, sometimes of great value, but it cannot alone be safely relied on to clear up the diagnosis without supporting data from other sources. The metabolic rate is increased also in fevers, in the essential anemias, in leukemia and in some forms of pituitary disease. W. S. McCann[1] remarks very conservatively: "Diagnosis must depend on other things than a metabolism test. A report of high or low basal metabolism has just the same kind of significance as a high or low leukocyte count. Both may be admitted as contributory evidence."

Moreover, the excitement of the patient at the ordeal of wearing the mask for ten minutes will sometimes run up the rate 30 per cent or more. And there are cases where a minus rate only indicates that the general health of the patient is down. One must also bear in mind the chance of leaks in the apparatus and mistakes in the mathematics—in short one must mix all the data of basal metabolism with a good proportion of common sense and clinical experience.

And there are atypical cases where now and then the diagnosis of hyperthyroidism or hypothyroidism seems clinically necessary despite the fact that the basal metabolic rate is not materially altered. H. O. Mosenthal[2] and Janney and Henderson,[3] for instance, mention such cases; the writer has also observed similar ones.

The *Complement-fixation Test* that I have already alluded to (p. 70) seems to be of diagnostic value in Graves's disease. Nothing but a Wassermann outfit is needful. In respect of results I have already written as follows:[4]

The total number of tests, diagnostic and control, amounts now to considerably more than 250—upon almost as many subjects.

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[1] Med. Clin. North America, March, 1921.

[2] Ibid.

[3] Arch. Int. Med., 1920, **26**, 297.

[4] Med. Record, January, 1922.

The controls have covered a wide range of ages, diseases and dyscrasias, except the acute infectious diseases. All the controls were negative except 1. The number of thyroid cases is about 85. Of these about 25 were chronic or subchronic goitres in which a hypothyroid condition was to be suspected. In only 1 of these did we get a positive result—due, possibly, to immunological conditions touched on below. Of the remaining 60, 50 reacted positively. In all these the clinical course of the disease seems to have borne out the diagnosis.

The positive tests have run all the way from 1+ to 4+, and in those cases where we had opportunity to examine the same patient at intervals of six months or a year the serum test has appeared to keep pace with the clinical course of the disease, the reaction disappearing when the patient had recovered or, as happens now and then, had passed over into a hypothyroid condition. Of the remaining cases it is probable that several were true toxic thyroidism, albeit the serum test was negative.

The occasional negative test in a true case is explicable on ordinary immunological principles, though many more cases must be observed before one can be reasonably assured of the correctness of this view.

One case, an adult female, in the care of a medical friend in New York City, developed the disease with fulminating acuteness. She was suddenly seized with dreadful nervousness, fever, tremor, tachycardia and exophthalmos, with a small soft thyroid gland. She died in a few days. Her serum was negative.

Another acute case, also a woman, living a few weeks, was negative until a few days before her death, when the serum was 2+. The explanation here seems to be merely that the patient's system was overwhelmed with toxic material; there was no time for the development of antibody. A similar case in my own practice, seen and tested three weeks after the appearance of active signs of toxic thyroidism, was negative. I have not been able to get another specimen of blood from this patient in order to verify the first test.

The common time allowance for the development of diphtheria antitoxin in horses is from four to six weeks and more; for sheep-cell antibody in rabbits, four weeks; the Widal reaction appears about the third week in typhoid fever, and is sometimes delayed until convalescence. We may reasonably anticipate some similar delay in the case of thyroid toxins in the human body.

On general immunological principles we may also expect that some patients under unfavorable physical conditions will make no antibody at all for a long time, and that again some patients will make such an excess of antibody that it will persist as such in the patient's serum, like the 4+ Wassermann in syphilis, long after clinical signs have disappeared.

This consideration probably offers an explanation of the 4+ reaction in the chronic goitre case mentioned above. This was a school girl, aged sixteen years, from Michigan. She had had an enlarged thyroid since her thirteenth year (probably endemic goitre), with a history of mild nervousness. But at the time she was sent to me (through the courtesy of Dr. J. Perry Seward of New York) she had no such symptoms. Her temperature was 98° F.; pulse standing, 84; there was no tremor, and her eyes were normally situated in the orbits. Her condition was in some regards more suggestively hypothyroid, and she did well on small doses of thyroid gland, and 2 gr. twice a day of potassium iodide. Six weeks later her thyroid had diminished in size, but the serum reaction was still 4+.

Evidently, therefore, the serum test, if it is to be really useful in diagnosis, must be considered as a part of the diagnostic symptom complex. It is not necessarily more pathognomonic than *Bacillus diphtheriæ* in the pharynx of a healthy "carrier" is of diphtheria.

The *Adrenalin Test* of E. Goetsch[1] has been proposed as of clinical value in diagnosis. L. F. Barker[2] approves it as a confirmatory sign. C. H. Mayo[3] declares it altogether too variable for clinical dependence. A recent report by M. S. Woodbury[4] at the Clifton Springs Sanitarium, of a number of cases in which the test was tried, concludes that an adrenalin injection reacting positively indicates a generally increased excitability of the sympathetic nervous system which may or may not be of thyroid origin. Irene Sandiford[5] injected 39 patients suffering with various disorders of the ductless glands forty-six times with 0.5 cc. of 1 to 1000 adrenalin. There was an invariable increase in the metabolic rate, but no relation was found between the intensity of the adrenalin reaction and the degree of hyperthyroidism or hypothyroidism. Marine and Lenhart[6] tried similar tests on groups of normal and of thyroidectomized rabbits, with similar results.

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[1] New York State Jour. Med., 1918; Barker's System, New York, Appleton, 1922.

[2] New York Med. Jour., 1921, **113**, 353.

[3] Surg., Gynecol. and Obst., 1921, **32**, 209. [4] Jour. Am. Med. Assn., 1920, **44**, 997.

[5] Am. Jour. Physiol., April, 1920.

[6] Ibid., December, 1920.

As to the Marine and Lenhart experiments, it should in fairness to Dr. Goetsch be noted that owing to the number of accessory thyroids in rabbits excision of the large glands may not always materially modify the thyroid metabolism. I do not think, therefore, that the summary dismissal of the adrenalin test on the above grounds in a recent editorial of the *Journal of the American Medical Association*[1] is as yet justifiable. The test requires a much more extensive try-out.

R. S. Dinsmore[2] says of the Goetsch test that "Its results cannot be used as a basis for estimating the operability or postoperative reaction of the patient." Yet Dr. Goetsch never suggested that the test could be used in this way. Dinsmore at the same time notes that as a means of differentiating border-line cases the adrenalin test has been of distinct value in Dr. Crile's Clinic; that 89 per cent of a series of patients with clinical signs of Graves's disease gave a positive reaction, and that in about 80 to 85 per cent of the cases the Goetsch test agreed with the metabolic findings.

The technique of the test is thus given by Dr. Goetsch:[3] "This test always confirms and usually establishes the diagnosis of hyperthyroidism ('hyperthyroidism' is used to include the Graves syndrome). When positive the test is an indicator of hypersensitiveness of the sympathetic nervous system. There is a small percentage of clinical conditions which give a more or less positive reaction and which are not dependent upon definite pathological changes in the thyroid gland. However the test is positive in all cases of hyperthyroidism. . . . With a negative test one can state definitely that hyperthyroidism is not present.

"The test is mildly positive when, after injection of 0.5 cm. of solution of epinephrine chloride (adrenalin chloride of Parke Davis & Co.), a rise of about 10 points in pulse pressure or in systolic pressure, or in both, is obtained, and certain clear-cut objective and subjective signs and symptoms of hyperthyroidism are brought out. Normal subjects do not react to this dose. . . . In one and a half hours the reaction disappears. . . . The patient should rest in bed at least a day previously. If this is impossible reclining for one-half to one hour may be sufficient." The adrenalin must be fresh. Tests of pulse, respiration and blood-pressure should be made several times before the injection, and every two and a half to five minutes after. "In exophthalmic goitre the reaction has been uniformly positive, and as a rule remarkably parallel in its manifestations with the severity of the disease." The author reports the test relatively negative in hypothyroidism, and thinks it of special value in distinguishing exophthalmic goitre from early tuberculosis. He commends it as easily performed, inexpensive and readily understood.

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[1] Editorial, Jour. Am. Med. Assn., 1921, p. 866.

[2] Crile and Associates: The Thyroid Gland, Philadelphia, Saunders, 1922.

[3] Loc. cit.

In patients with high blood-pressure it should not be used. Dinsmore[1] noted that in one patient the blood-pressure rose from 168 to 260 mm. systolic.

Blood-sugar Test.—The *rationale* may be inferred from previous paragraphs (p. 70). The test is made by giving the fasting patient a maximum dose of carbohydrate (glucose) and noting the blood sugar for three hours afterward at convenient intervals. As a rule, 100 gm. of glucose given to a fasting man of 70 kg. weight will have no prolonged or material effect on the blood sugar. In patients with Graves's disease normal figures (0.09 to 0.12 per cent) will be considerably exceeded, and in some cases sugar will appear in the urine. The blood-sugar methods of Benedict and Folin are clinically reliable. The technique is given in the text-books. But there are many other chronic and temporary conditions which increase the blood sugar. A positive report can only confirm a diagnosis previously thought probable.

Abderhalden's Ferment Test.—Lampe, Arno and Papazolu[2] affirmed that in 25 cases of Basedow's disease the patient's serum gave the ninhydrin test. Admission is made that controls were insufficient. Recent American references to the *Abwehrfermente* are hard to find.

Acetonitrile Test.—R. Hunt's[3] acetonitrile test of thyroid efficiency was at one time supposed by him to be available as a test of the supposedly increased amount of thyroid in the blood in Graves's disease.[4] His test was arranged in this way:

Five cracker-fed mice received increasing doses of acetonitrile.
Five blood-fed mice received increasing doses of acetonitrile.
Five Graves-blood-fed mice received increasing doses of acetonitrile.

The first 5 began to die at a level of dosage of 0.37 mg. of nitrile per gram of body weight; the second 5 at a level of 0.38 mg.; the third 5 at a level of 0.75 gm. The goitre blood thus appeared to produce the protective effect that thyroid gland produces. There is quite a mass of literature on the subject up to the time of Hunt's last paper.[1] He comments on the favorable results of Ghedini, and on the curious observation of Trendelenburg that the blood of thyroidectomized cats gave the same results, and after describing some further work of his own concludes very conservatively: "Additional experiments show that the blood in certain pathological conditions (especially those in which the thyroid is involved, but also in nephritis) contains unknown or unidentified substances which markedly increase the resistance of mice to acetonitrile."

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[1] Loc. cit.

[2] München. med. Wchnschr., July, 1913, p. 1533.

[3] Loc. cit., p. 53.

[4] Jour. Am. Med. Assn., 1907, **49**, 240.

Kottmann's Test.—K. Kottmann[2] has devised a serum test which depends upon the experimentally discovered fact that the blood in hyperthyroidism exercises a more complete colloid protection upon another colloid than normal blood can.

The patient fasts for twelve hours. He should have taken no bromine in any form for two months previously. The serum is prepared as for a Wassermann test. In a dark room, with a ruby lamp, to 1 cc. of the patient's clear serum are added 0.5 cc. of 0.5 per cent of KI solution and 0.6 cc of 0.5 per cent of $AgNO_3$ solution. Mix without bubbles. Of normal human serum 1 cc. is prepared in the same way as a control.

The two tubes, now containing a colloidal suspension of AgI, are exposed for fifteen minutes to a 500-candle-power light at a distance of 25 cm. One cubic centimeter of 0.25 per cent hydrochinon is now added (again in a dark room). A change of color to reddish-brown occurs in the control (normal) serum in about five minutes. Hypothyroid sera show the color sooner; hyperthyroid sera do not change in less than one-half hour. The hydrochinon is a developer. The light reduces the silver partly; the hydrochinon completes the reduction to metallic silver. F. D'Oubler[3] has stated that with this test 57 of 58 clear cases of Graves were positive; 14 of 15 border-line cases were positive; 20 supposed normals were negative.

Hypophysis Test.—Claude, Baudouin and Porak[4] made an alcoholic extract of posterior lobe of beef hypophysis. They evaporated this and redissolved it in aqueous saline, so that one-half of one beef gland was represented by 1 cc. of the solution. By injecting this amount in patients with Graves's disease they found that the pulse was slowed from 10 to 48 beats per minute. I have no experience with this test.

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[1] Loc. cit., p. 53.
[2] Schweiz. med. Wchnschr., 1920, **1**, 644.
[3] Crile and Associates: The Thyroid Gland, Philadelphia, Saunders, 1922.
[4] Bull. et mém. soc. méd. des hôp. d. Paris, 1914, **37**, 1094.

Loewi's observation,[1] that adrenalin will dilate the pupil of patients with Graves's disease more quickly than occurs with normal eyes is related to the principle utilized in the Goetsch test.

Therapeutic Test.—This consists merely, when other data fail, conflict or are unavailable, in giving thyroid extract. If the patient reacts violently and quickly to a few small doses we have grounds for thinking that the supply of thyroid in the system is already excessive, that is, that the patient is already in a hyperthyroid state. Reasonable care must be exercised in the selection of cases. The initial dose should not be more than $\frac{1}{8}$ gr. of desiccated gland. Normal men can usually take this dose by mouth two or three times a day for several days and not feel more than a slight increase in well-being. In hyperthyroid people signs of thyroid intoxication (p. 114) appear promptly. Idiosyncrasies detract from the value of this test. I have seen apparently normal young men who uniformly had a violent and disagreeable reaction within an hour after taking $\frac{1}{10}$ gr. of a good preparation of dry thyroid.

Course of the Disease.—Prognosis.—Graves's disease begins, progresses and terminates in many ways. The fulminating cases have been mentioned (p. 68) in which the symptoms develop with great speed and are rapidly fatal. In some instances within a day or so the thyroid develops into a soft swollen doughy mass, the eyes start, the temperature rises to a considerable height, the pulse runs up to 160 and higher, strength and flesh waste, and the patient dies in a few days with signs of a profound general toxemia. Fortunately these cases are very unusual.

Commonly the disease develops in the course of weeks or months with a rapid pulse, a slight temperature and a general sense of fatigue and breathlessness. A thyroid swelling appears about the same time, and the eyes acquire a stare. Treated conservatively with rest, careful feeding and symptomatic medication these patients often improve within three to six months, and are virtually well again in a year. Relapses are common.

More obstinate cases are better and worse for years, and after an indefinite lapse of time (three to five years) the disease may pass over slowly into a *hypothyroid* condition, with some or all the symptoms described on page 108. In these chronic cases organic changes in the thyroid, the orbit and the heart are apt to persist, and the immediate diagnosis becomes one of considerable difficulty.

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[1] Wien. klin. Wchnschr., 1907, **20**, 782.

The symptoms are apparently contradictory.[1] They are, however, I think, always finally explicable when the history of the case is available. Some chronic cases have alternating states of excessive and diminished thyroid activity, imitating the alternating mania and melancholia in circular insanity.

There is general agreement among conservative clinicians that with intelligent expectant treatment 50 per cent of the cases will recover. This is my own experience. The fact that the *vis medicatrix naturæ* is so efficient in Graves's disease makes one wonder whether the innumerable remedies for the disease do not owe their reputation mostly to this natural beneficent recuperative power.

Finally the most distressing cases of all must be mentioned—those patients who have been injudiciously operated on, overtreated with roentgen-rays and have taken almost all the drugs in the Pharmacopœia. These patients become nervous wrecks, going about from one specialist or clinic to another, emaciated, trembling, anemic, depressed, temporarily better under any new treatment and later relapsing again, until some intercurrent fatal malady ends their sufferings. Their symptoms are perplexing and contradictory. As a description of their condition the term *chronic toxic thyroidism* seems to have some clinical justification.

Treatment.—*Prevention.* Intelligent care in anticipating the development of this disease is often very effective. All preventive measures relate ultimately to the prevention of simple goitre. The avoidance of overstrain and the value of prophylactic doses of iodine have been fully discussed in the section on Goitre. In regions where goitre is endemic, community endeavor seems to be the ideal method. When this is not practicable, the family physician should impress upon his personal *clientèle* the necessity of preventive doses of iodine during the susceptible period. The earliest stages of a simple goitre actually in evidence are also amenable to the iodine treatment. Here, however, more care must be exercised, particularly if iodine be given in the form of thyroid extract. If Graves's disease be actually impending, the least bit too much of thyroid extract may precipitate the attack. Therapeutic details of thyroid administration are to be found on page 110.

Treatment of the Active Disease.—Removal of Predisposing Causes.—The general axiom of treatment that the cause must be removed is not perfectly applicable here, for the cause is in dispute, but no one will question that accessory and predisposing causes should carefully be looked for, and as far as possible removed, in order to give the natural recuperative power of the patient a fair chance. A review of previous paragraphs (p. 65) will give a satisfactory notion of what may be attempted. The condition of the stomach, bowels and gall-bladder, the chances of chronic appendicitis, the existence of bad tonsils, defective teeth, catarrh of the urinary bladder, renal pelvis, nasal sinuses, middle ear, must be systematically determined, and the proper medical or surgical remedies applied. Roentgen-ray photographs should be a routine source of information. The study must be conservative and not too hurried; supposed facts must be verified by more than one examination. Routine tests of the blood and urine and a Wassermann test are always necessary. That a complete physical examination should be made goes without saying.

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[1] Bertine, E.: Med. Rec., 1916, **90**, 895.

Hygienic Measures.—Probably the first, the most important and most generally recognized necessity is *rest.* This includes not only absolute physical rest in bed, with the help of an intelligent nurse in the matter of food, daily bath and dressing of the patient's hair, but protection from mental worry, relief from household cares and the interdiction of visits from well-meaning friends. *Fresh air* is a *sine qua non* also.

As these conditions are often not attainable at home, a rest cure in the country, or in a sanitarium or well-conducted hospital should be advised. The patient should be fed an abundance of simple food in the usual balanced allowance of 1 part by weight of protein, 1 of fat and 4 of carbohydrate. Some clinicians urge the relative diminution of protein, but the basal metabolic studies of careful observers do not seem to indicate that this has any special advantages. A gain in weight is, as a rule, desirable, and a full allowance of calories plus 10 per cent should be directed. The proteins of meat, milk and egg seem to be more easily taken care of than vegetable proteins. The patient should be weighed at regular intervals. In thin patients a gain in weight is a favorable sign.

In cases of average severity it has been shown by a vast number of metabolic tests that rest in bed, good food and protection from anxiety will on the average reduce the basal metabolic rate in the first week about 10 per cent. Recovery happens so often by following out this line of treatment alone that one should persevere in it for at least six weeks before advising any more drastic or questionable measures. Not only the basal metabolic rate falls but the pulse is less frequent, the tremor is improved, nervousness allayed and assimilation of food greatly increased.

Simple accessory measures are, of course, at times of value. The bowels very generally need attention, and a large daily rectal injection of warm bicarbonate solution is the best assurance of a comfortable daily stool. About 4 gm. of sodium bicarbonate to the liter of water may be used—roughly a teaspoonful to the quart. Sometimes the enema should alternate with a mild saline purge.

By some physicians the daily colonic flushing has been described as the essential means to a cure. But none of the proponents of this "cure" have neglected to put their patients to bed and secure physiological rest.

When the heart beats violently, an ice-bag placed intermittently over the precordial region, the manubrium, or the thyroid gland itself will do no harm if the patient likes it. If she objects it is generally best to avoid controversy by yielding to her wishes. Eye-strain is to be guarded against; some physicians emphasize the importance of a darkened room.

Care of Convalescence.—The experienced physician will be able to apply the usual principles of treatment in such cases without special instructions. Properly arranged travel may be beneficial. Instead of entire idleness, a slow return to some useful occupation may be desirable. When the patient is well on the road to recovery there is no objection to marriage. Some writers think it positively beneficial. Until recovery is complete the strain of pregnancy and lactation should be avoided. In countries where it is legal to do so instructions as to birth control should be given.

Medication.—Possibly no disease in the range of medicine has been treated with such a variety of remedies. As one looks over page after page of the current text-books and notes the preposterous accumulation of drugs warranted to relieve and cure exophthalmic goitre (each suggestion backed up by a long series of case histories and a learned bibliography) one is tempted to exclaim with Sir William Hamilton, "There is no opinion which has been unable to obtain not only its votaries but its martyrs." D. Marine is credited with the statement that in the literature of the subject cure has been attributed to each of 239 drugs and other methods of treatment.

Not to show, however, too great an irreverence for constituted authority one must enumerate a few of the medicines commonly recommended.

Iodine.—On another page it has been already stated that S. P. Beebe[1] noted in chemical analyses of thyroids removed in Graves's disease a deficiency of iodine, and that this has been confirmed by other students. One might then reasonably infer that giving iodine would be of therapeutic value, and Beebe reported that clinical results bore out the supposition. He recommended doses of very small amount, not more than 1 gr. a day. But there are many cases which appear to be inaccessible to any chemical aid which iodine can give. Some of my patients get promptly worse, even on small doses. From the Mayo Clinic Boothby and Plummer[2] reported that in a recent large series of cases (over 600 in all), including some of a very violent and alarming character, Lugol's solution in 10-drop doses, diluted, and followed by half a glass of water was administered once or twice a day. The heart-beat and general condition were very much improved, and operation was was undertaken afterward with greater confidence and success. McCarrison[3] recommends an inunction, directly over the thyroid gland, of diluted red iodide of mercury. One wonders whether massage of the gland might not liberate a dangerous amount of toxic secretion. Marine and Lenhart in 17 cases found iodides of value. They gave syrup of ferrous iodide in 5-minim doses once daily for a week, and then gradually increased the dose to 20 minims a day.

The *cardiac stimulants,* digitalis and strophanthus, are said by many to be of value in moderating the violence and speed of cardiac action. The tinctures or other standard preparations of these drugs may be tried in suitable doses when they are indicated. They should be stopped at once if the stomach or bowels show signs of irritation; no remedy is of value in this disease if it retards or disturbs digestion. N. S. Shofner[4] says that in Crile's Clinic tincture of digitalis is a routine preoperative dose—2 cc. every four hours for eight doses and that it is an indispensable aid in improving the state of the myocardium and the kidney function. It seems not unlikely that digitalis got its reputation from its successful use in patients previously affected with valvular disease, or who developed it in the course of their thyroid trouble. McCarrison[5] urges that it should never be employed otherwise. Mackenzie has long maintained that digitalis does no diseased heart any particular good except when auricular fibrillation appears.

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[1] Loc. cit., p. 69.

[2] Collected Papers of The Mayo Clinic, 1923, **15**, 565.

[3] Loc. cit., p. 61.

[4] Crile and Associates: The Thyroid Gland, Philadelphia, Saunders, 1922.

[5] Loc. cit.

Belladonna has also its advocates. They urge that it or its alkaloid, atropine, is in some ways a physiological antagonist of the sympathetic nervous excitement noticed in Graves's disease. These writers direct it to be given until the throat is dry and sweating has been entirely arrested.

Forchheimer's Treatment.—Forchheimer[1] recommended a combination of ergot, which was intended to reduce the blood supply to the thyroid, and the hydrobromide of quinine, which he thought a specially efficient sedative in this disease. This mode of treatment really seems to be of value sometimes. It has appeared to me to improve the condition of certain patients who had been stationary under previous methods. Forchheimer recommended ergot or ergotine, 1 to 1½ gr., and the quinine hydrobromide was advised in capsule form, 5 to 10 gr., three or four times a day. Many patients tolerate this dose for a surprising length of time without cinchonism or bromism. I never saw it do any good when the patient's ears began to ring and bromide acne appeared in the first few days of treatment. In later cases where the blood-pressure is raised the ergotine should certainly be omitted. Indeed there is doubt whether it is ever essential to the Forchheimer "cure." Jackson and Mead[2] reported a series of cases treated in this way, 56 in all, in which 76 per cent were cured (two years afterward) and 13 per cent benefited.

Symptomatic remedies may be useful from time to time. It is not necessary to enumerate them.

As to *endocrine antagonists* and *adjuvants* of the excited thyroid, scientific theory is very vague, and suggested lines of treatment are empirical for the most part. Commercial preparations of the dried blood and milk of thyroidectomized animals I have never used. On another page (p. 241) is noted the experience of Shapiro and Marine with fresh adrenal cortex. Adrenal medulla not only disturbs the stomach (if given by mouth) but by hypodermic aggravates all the sympathetic symptoms of the disease exactly in proportion to the size of the dose. Thyroid extract is poison. Ovarian extract has no beneficial effect on Graves's disease, unless there is some complicating condition of the ovaries that demands it. Thymus is recommended, and in the literature the usual long series of benefited and "cured" cases may be found reported. It is hard to see why thymus should be indicated in Graves's disease. The gland is already enlarged and vascular in many of the cases. It may serve some useful purpose as a *placebo*.

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[1] Therapeusis of Internal Diseases, 1st ed., New York, Appleton, 1906.

[2] Boston Med. and Surg. Jour., 1908, **158**, 346.

Care of Fulminating Cases.—But little of an encouraging nature can be reported of the treatment of these cases. Absolute repose in a dark room and the local use of the ice-bag are, of course, indicated. Lugol's solution (p. 90), opiates and bromides may be tried. Promotion of elimination by copious water-drinking or saline infusions, by enemata and sweating may possibly improve the patient's condition to a point where a ligation (with a local anesthetic) may be ventured upon. Death is often sudden, and not generally long delayed.

Use of Basal Metabolism.—Therapeutic efforts of whatever character are usefully controlled and regulated by periodic tests of the metabolic rate. In Chapter III a brief résumé of methods has been given, and on p. 78 will be found a statement of the degree and limits of the increase in metabolism which may be expected in the Graves syndrome. Metabolic laboratories or smaller instalments are now available in the cities and larger towns of this country. During the rest treatment, during roentgen-ray exposures, during the experimental use of new and the routine use of routine remedies the basal metabolic rate is a valuable resource. Interpretation of the figures must be conservative, and must be continually checked up against clinical signs of improvement or the reverse. Successive figures with the same apparatus on the same patient are more comparable with one another than when general averages alone can be relied on for a norm.

Serum Treatment.—The antithyroid serum of Moebius (said to have been derived from the blood of cretins) and the thyrolytic serum of J. Rogers and S. P. Beebe[1] were intelligent and interesting efforts to apply serological methods to the problem of reducing the size and activity of the thyroid in Graves's disease. For a time great hopes were cherished that the latter resource might offer a solution of the problem. But later results have not been better than those of the rest treatment. I believe cytolytic therapy has been generally abandoned.

Surgical Treatment.—It is not the object of this book to treat the surgical aspects of endocrine problems with minute attention. But from the point of view of prognosis and availability some comment is required.

It is needless to go into the discouraging figures of operative mortality for thyroidectomy in Graves's disease in former years. Here it will be enough to say that surgical methods have nowadays

[1] Arch. Int. Med., 1908, 2, 297.

a secure place in the treatment of many cases and that the mortality from the operation now done by experienced specialists has been rapidly reduced from the old figures of 25 per cent and over to the present figures of 1.5, 2 and 3 per cent.

Operative interference may be by *ligation of one or both thyroid* arteries on each side, by *thyroidectomy*, or by a preliminary palliative ligation followed by thyroidectomy when the patient's condition has improved enough to justify the greater risk. Ligation may be done with a local anesthetic.

Thyroidectomy is always a major operation. Operative and postoperative complications are by no means few. Collapse of the trachea may necessitate tracheotomy. Inhalation of blood may be followed by fatal pneumonia. Wounds of the recurrent (motor) nerve to the larynx are followed by paralyses of various kinds, of which double abductor paralysis is a menace to life. Damage to the parathyroids or their blood supply may result in postoperative tetany. A peculiar "postoperative reaction" of fever and tachycardia may be fatal. Removal of too much thyroid may result in myxedema. In America, however, this accident is extremely rare (only 1 to 500 cases is claimed in Crile's Clinic at Cleveland).

The old-fashioned operation of removing the larger lobe (originating, I believe, with Kocher) is apt to be followed by a disfiguring hypertrophy of the lobe left behind. If the isthmus alone is left it often develops into an immense "Adam's apple," which to young women especially is extremely disconcerting. The modern thyroidectomy operation aims to leave a small part of the posterior border of each lateral lobe behind, and remove everything else. This spares the parathyroids also. The remaining parts of the gland in favorable cases hypertrophy physiologically until they become equal to the normal demand.

In my experience cases of Graves's disease in which the thyroid is not enlarged are not improved by operation. Statistics on this point are hard to find, but I believe the fact is now rather generally recognized.

The results of surgical interference, even in properly selected cases, have not always been stated without prejudice. Many deaths occur which are classed by the surgeons as "non-operative." Many of the cases are lost after operation and the statistics of recurrence are not reliable. All the cases operated on get a prolonged rest cure afterward. The curative effect of operation *per se* is also to be recalled to mind. Even the operation at one time popular of removing the superior cervical ganglion of the sympathetic for relief of exophthalmic goitre was followed by a series of "cures."

Operations for the removal of the thymus gland in this disease have been also urged. W. S. Halsted[1] wrote up the subject, and quoted the very unconvincing literature; one hears but little of it to-day.

Roentgen-rays.—Roentgen-ray therapy has been extensively used as a means of reducing the size and activity of the Graves goitre. The literature is large. Ludin[2] collected references to 208 papers on this topic, and there are hundreds since.

The advantages of the procedure have been summarized by Seymour and Malcolm[3] as follows:

There are no fatalities.
There is no resulting scar.
Treatment does not interfere with the patient's occupation.
It is painless, and causes very little inconvenience.
If unsuccessful, an operation may be done later with less difficulty.

Means and Aub[4] declare that roentgen-ray treatment is "as good as surgery in cases of equal toxicity," and that surgery should be employed only when other means have failed.

On the other hand, Pfahler and Zulick[5] affirm that by reason of the imperfections and guess-work of the technique statistics from different observers are not comparable with one another. Otto Hildebrand[6] in 13 cases got no satisfactory results of a permanent character, and says that subsequent operations were much more difficult. He also mentions that fatalities have resulted from "thyroidismus"—acute swelling of the gland after exposure. In respect of Seymour and Malcolm's claims it must be also noted that scarring is by no means unknown, and that far from causing "little inconvenience," the patients have sometimes an alarming and violent reaction lasting for days, with great loss of weight and profound toxemia.

Admitting that the accidents above mentioned may be due to bad technique, we have the further objections of C. H. Mayo[7] that in his experience benefits were temporary or entirely absent, relapses were frequent, and overdosage, with hypothyroidism as the final result, was an accident hard to foresee or guard against. In the present writer's observation of roentgen-ray treatments the last objection is the most cogent of all.

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[1] Loc. cit., p. 69.
[2] Centralbl. f. d. Grenzgb. d. Med. u. Chir., 1915, **18**, 205.
[3] Boston Med. and Surg. Jour., 1916, **175**, 568.
[4] Arch. Int. Med., 1919, **24**, 645.
[5] Am. Jour. Roentgenol., 1916, **3**, 63.
[6] Arch. klin. Chir., 1919, **111**, 1.
[7] Surg., Gynec. and Obst., 1921, **32**, 209.

The value of roentgen-ray treatment is still, however, under discussion. Until the technique of exposure is perfected, it is safer to withhold judgment. Halsted[1] reported good results from roentgen-ray exposures of the thymus.

Radium Therapy.—Radium therapy also has its advocates. For details and dosage the papers of the technicians may be referred to. The action of radium is in a general way similar to that of the roentgen-rays. Dawson Turner[2] reported good results with radium in all but 1 of upward of 50 cases.

3. CRETINISM.

Synonym.—*Congenital athyrea.*

Definition.—Cretinism is a condition due to complete congenital defect or absence of the thyroid gland. The derivation of the word is obscure. French and German writers use the same word (*cretinisme, der Cretinismus*). When the condition first appears some years after birth, but before puberty, it is still by some authors rather loosely spoken of as cretinism. McCarrison urges that non-congenital cases should be called *infantile, juvenile* or *adult myxedema.*

Range.—As *sporadic cretinism* the disease appears anywhere. As *endemic cretinism* it appears with special frequency and severity in those regions of the earth where other forms of goitre are common and severe. Probably today the worst endemic regions are the mountain valleys of Switzerland and India. On the contrary, the zones in the United States where benign goitre exists, atacking in the main only adolescent girls, show hardly any greater incidence of cretinism than is to be found in the rest of the country. Sufficient notice of "endemic centers" of cretinism will be found in the account of the same question in goitre (p. 57).

As regards frequency, sporadic cretinism in America is a rare disease.

Pathology and Morbid Anatomy.—The essential lesion is congenital absence or a complete congenital secretory incompetence of the thyroid. Congenital absence may be explained or at least classified as a developmental error. Secretory incompetence is secondary to destructive disease. While in theory ordinary tumor formation, or a destructive inflammation like syphilis may be the trouble, clinicians are practically well convinced that cretinism is most often due to the same causes that produce simple goitre. At autopsy the site of the thyroid may be occupied by a small cell-infiltrated scar, or a larger mass, a goitre, may be present in which fibrous tissue, cysts and calcareous patches have entirely destroyed and replaced the epithelial parenchyma. Appearances elsewhere are secondary. The body has failed to develop, and metabolic processes have been slowed up or arrested. There is an uneven deposit of fat under the skin, and often a subcutaneous and visceral infiltration with a mucinoid substance. The exact chemistry of this substance is unknown. It produces what is commonly called a myxedematous infiltration. The bones, sex organs and nervous system all participate in the failure of growth, and the organs of sense are deficient. These points will be more conveniently explained in the paragraphs on Symptoms.

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[1] Bull. Johns Hopkins Hosp., 1915, **26**, 55.

[2] Edinburgh Med. Jour., 1919, **22**, 79.

Predisposing Causes.—Sex does not appear to be of much consequence. Some writers report that more boys than girls are affected. Children born in severe endemic centers are more apt to be cretins. Mothers who have had goitre, or mothers who develop goitre during pregnancy are more apt to bear cretinoid offspring. Children born of a mother with Graves's disease are also more apt to have some thyroid trouble, though it may not be so severe as cretinism. The effect of thyroid deficiency in the parents upon the offspring has been curiously shown by the experiments of Halsted on bitches.

Symptoms and Signs.—McCarrison has described carefully the appearances noted in 203 cases of endemic cretinism in India. He thinks the cases can be classified into two general types, myxedematous and nervous cretinism. The grewsome picture he draws of human wretchedness is fortunately not to be seen in the Western World. Physicians in the United States know almost nothing by personal experience of the half-human horrors that this author tells of. In the nervous class he has placed a number of cases with spastic paralysis and tremors—some combining these symptoms with the ordinary signs of myxedematous cretinism. He thinks that the nervous manifestations described are due not to cerebral hemorrhage or birth palsy, but are direct results of athyroidism. In 1 case at autopsy he was unable to find the parathyroids. The author's account[1] may be consulted for further details and for photographs of the patients. Cretinism as it occurs in America is very generally of the myxedematous type.

As regards the thyroid at birth there is often nothing visibly or palpably wrong. During the nursing period the child presumably gets some help from minute amounts of thyroid secretion available in the milk, unless nursed at the breast of a hypothyroid mother. The child's thyroid may or may not enlarge during the first or second year. There are cretins with and cretins without a goitre. Indeed it is said that with the appearance of a goitre the child's general condition may improve. But before the first year has passed even the dullest parent recognizes that something is wrong with the baby, and by the end of the second year the diagnosis is unmistakable.

The infant gives few signs of intelligent response to his surroundings. He makes only automatic reactions to stimuli. The head is relatively large, as a rule; the fontanelles, which ought in normal babies to be closed by the end of the sixteenth month or thereabouts, remain open long after the second year has ended. The lips are thick, the tongue is thickened and often protrudes from the mouth; the malar bones are prominent (Figs. 22 and 24). The stature is dwarfed; the legs short and bent. The mental condition is one of complete idiocy or imbecility. More than one-half of all cretins are said to be deaf, or mute, or both.

The teeth are slow in their eruption, atypical in location, badly shaped and deficient in enamel. They easily decay. The mucous membranes are prone to inflammation; bronchitis, coryza, bowel troubles and cystitis are common. The cretin, like other idiots, is untidy in his habits. The skin is rough and dry; the hair dry and coarse; the oil and sweat glands act imperfectly; the temperature is subnormal. McCarrison[1] remarks that the sensibility of the skin is impaired, and that among the neglected children of the poor burns, scalds and other injuries are common.

The child does not appear emaciated, but the subcutaneous fat is irregularly disposed in pads—over the clavicles perhaps, or about the legs. When the mucinoid infiltration appears it is not always evenly diffused, but may give a specially swollen look to the belly, or arms, or legs. It is a useful diagnostic point that this swelling does not pit typically on pressure. The belly is protuberant, hernias of various kinds are observed and in males the testes may fail to descend.

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[1] Loc. cit., p. 61.

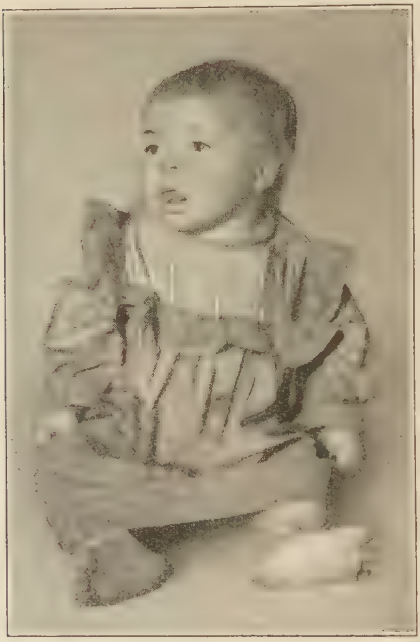

FIG. 22.—Case of sporadic cretinism, aged four years. Beginning of thyroid treatment. (Jelliffe and White.)

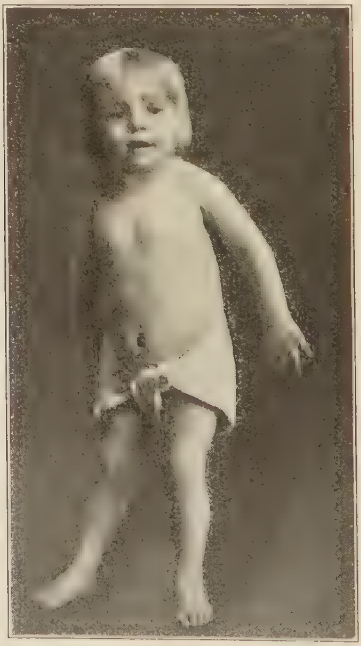

FIG. 23.—Case of sporadic cretinism, aged five years. Thyroid treatment for one year. (Jelliffe and White.)

For evident reasons such children are very susceptible to bacterial infections. Many die young.

Diagnosis.—Osler remarked a good while ago: "The diagnosis of sporadic cretinism, though easy in advanced and typical cases, is often, I find, not clearly made; I judge this from the many descriptive cases sent me as instances of this condition, which in reality have been cases of various (other) forms of idiocy." Cretinism may be confounded with Mongolian idiocy, with achondroplasia, with physical dwarfism (Chapter XV), with chronic epilepsy and (by the inexperienced observer) with defective mental states resulting from birth injuries of various kinds and from cerebral tumors and inflammations. The wide dissemination of the information in the present generation of physicians that cretinism is curable by thyroid extract makes most physicians try thyroid on almost all the backward children brought to them. And as thyroid has a slight stimulative effect on many such cases (of the most diverse etiology) the confusion is sometimes perpetuated in this way. It ought to be possible to recognize the Mongol by his peculiar facies, red eye-lids, relaxed joints and short little finger. Patients with achondroplasia are sexually well developed and mentally rather alert, never idiotic, as far as I have observed. The various types of dwarfs have often a good mentality, and nothing except their stature to stigmatize them as abnormal. Chronic epilepsy must be distinguished by the frequency and character of the fits. In the sporadic cretinism of this country fits are very unusual, certainly chronic recurrent fits are. The backward children with paralytic stigmata carry their tags on them. Perhaps the condition of the skin and connective tissue offers the most valuable differential sign. As a last resort there is no objection to the therapeutic test with thyroid. The clinical improvement should be immediate and remarkable. The basal metabolism test is in theory a valuable resource, but in the case of restless children it is impracticable.

Prognosis.—When the disease is recognized before the end of the second year, and proper treatment is persistently carried out, the change for the better may be quite miraculous (Figs. 22 and 23). Cases first treated around the tenth or twelfth year are usually so far behind normal children of their age that only relative improvement may be expected. After the fifteenth or twentieth year growth is no longer possible, unless the epiphyses of the long bones have failed to unite with the diaphyses. This question may be readily answered by making a few roentgen-ray plates. But some mental advancement may be still hoped for (Figs. 24 and 25).

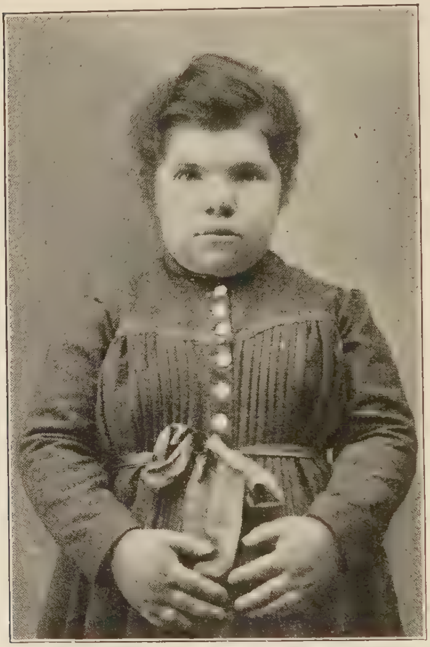

FIG. 24.—Case of sporadic cretinism, aged twenty-one years. Before treatment. (Sanderson.)

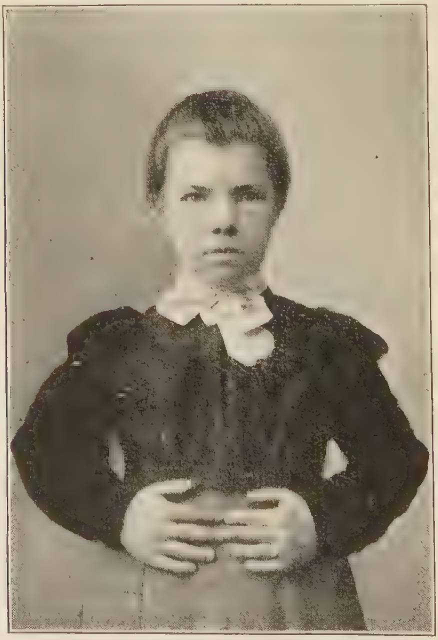

FIG. 25.—After four months' treatment. The same. (Sanderson.)

On the whole, however, cretins can never by the present methods of thyroid medication be brought to the normal mentality of children of the same age. This conviction, which has been reluctantly reached by long personal experience on my part seems to be generally concurred in by other independent students of the subject (Section 6). At the same time the remedy is of great value. It can render an otherwise hopelessly idiotic child capable of a moderate amount of education. Instead of being confined to an institution at the expense of the state, he can earn his own living in some minor position, such as doorman, laborer, dishwasher, painter, or gardener. The women of the poorer class can be taught sewing or housework of the simpler kinds. I have never known one of either sex who could take care of money when required to deal with dishonest strangers.

Treatment.—Of course the most encouraging results are gotten from patients whose condition is recognized early. All the details and anomalous reactions of thyroid therapy are to be found in Section 6. The patient should be kept under constant supervision. Among the ignorant poor in our large cities the mothers have to be visited frequently by the district nurse, that a supply of tablets may be kept on hand and *given to the child* instead of being thrown out of the window. In the ungraded classes of the public schools in New York the teachers have been always patient and tenderhearted coadjutors of the efforts made at my Clinic, even consenting to keep the bottle of tablets at school, and administer the dose themselves as directed.

In cases of complete absence of the thyroid gland the remedy must be given throughout life in appropriate doses. In less severe cases intermissions of treatment do not seem to do so much harm, for the remnants of thyroid gland still remaining in the neck are themselves stimulated by thyroid treatment. What may be practically expected from prolonged and intelligent medication I have already noted under Prognosis. Thyroid may often be usefully reënforced by other glands (p. 345).

It need hardly be added that far more than giving thyroid is required in the actual management of these cases. Hygienic conditions have to be looked into. When the patient lives in a goitrous region and the parents' means admit of it, he should be moved to a more favorable locality. All complicating conditions (among the poor their name is legion) must be remedied. The teeth must be attended to, tonsils and adenoids cared for, food regulated and bowels watched. The child should be regularly measured and weighed. After a preliminary loss of weight, thought to be due to disappearance of the pathological edema, gain in weight (and in height) should be rapid and continuous. In later treatment loss of weight usually means too much thyroid.

Enuresis should be carefully and patiently dealt with, and the punitive cruelties of unnatural parents softened as far as possible.

4. MYXEDEMA.

Synonyms.—The word is derived from two Greek words that have done duty in many other medical emergencies—one meaning mucus and one, swelling. Date and occasion of the introduction of the term have been mentioned (page 45). Other descriptive phrases are *athyrea acquisita, cachexia strumipriva* or *thyreopriva, major hypothyroidism.*

Definition.—Myxedema is a general disease caused by a high degree of acquired thyroid incompetence. Clinically the distinction between major and minor hypothyroidism is quite marked, albeit there is no hard and fast line of distinction between them. Minor thyroid incompetence is treated in Section 5.

Age and Sex.—It has been already noted that major thyroid incompetence may appear at birth, in childhood, in youth or in middle or old age. The congenital form has been already described as cretinism. The acquired form (myxedema) most commonly comes on after adult years have been reached. This form will be taken as a type for description, and peculiarities associated with other ages will be noticed afterward. As to sex, the cases are commoner in women, and perhaps a majority of the female cases fall about the time of the menopause.

Regional Distribution.—The disease is perhaps a little more common in cold than in hot climates. In regions where endemic goitre prevails myxedema also appears, but is not relatively so common as might be supposed. Sporadic cases appear everywhere. The actual frequency of the disease is rather hard to estimate, and owing to the greater familiarity with the early appearances among the better instructed physicians of this generation, gross manifestations of extreme myxedema are much less commonly seen nowadays than formerly. Postoperative myxedema is mentioned on p. 93.

Morbid Anatomy.—Findings at autopsy vary with the severity and duration of the disease. The thyroid may be found present only as an atrophic remnant of inflamed connective tissue. In cases preceded by goitre the thyroid changes occurring in that disease will be found. Usually they are so advanced that cystic degeneration, dense fibrous masses and blocked arteries have virtually destroyed the thyroid parenchyma. Unchecked hemorrhage, with resulting pressure effects, may be the immediate cause of death, as in simple goitre.

Secondary changes in the body due to depressed metabolism are generally similar to those described under cretinism, except that in adults growth is no longer a factor in the sum total of damage. Myxedematous infiltration of the subcutaneous tissues and of the viscera proceeds to various degrees. Irregular deposits of fat occur. Trophic changes in the nails, hair and skin are to be observed. They are mentioned more precisely under Symptoms. Damage to the parathyroids from pressure or arrest of blood supply is an occasional complication (Chapter V). Postoperative cases may be identified by the scar and the history.

Symptoms and Signs.—An excellent and realistic account of the general impression made on the observer by a patient with myxedema was given by Sir William Gull many years ago and is quoted on page 44. A more particular account follows.

Skin and Its Appendages.—The British Myxedema Commission (p. 45) reported on the condition of the skin and subcutaneous tissues in this disease. The exact chemistry of the myxoid infiltration is not understood. Its distribution is rather apt to be patchy—on the feet, ankles, wrists, face or shoulders. The skin itself is dry and rough. It may be scaly. Various cutaneous eruptions, such as psoriasis, eczema (in small children milk crust) and acne may appear. Pigmentation, leukoderma, warts and even ichthyosis have been reported.

The scalp hair is dry and ill-nourished. It may turn prematurely gray; it may fall generally, or in special places, such as the parts along the brow, at the back of the neck ("cassowary neck") or at the outer ends of the eye-brows. Axillary and pubic hair may also fall. Yet one should regard such symptoms with due skepticism until they are confirmed by signs of myxedema elsewhere; for the hair suffers also in exophthalmic goitre and various other endocrine diseases; many cases of general and localized baldness in men and women are entirely unrelated to thyroid trouble.

The nails may be wrinkled, striated and brittle. The face is often immobile and expressionless, and the eye-lids may be puffy. The color of the face is a little waxy in some patients, suggesting anemia or Bright's disease. The hands are thickened and "spade-like," and manual dexterity is impaired.

Mucous membranes share in the metabolic depression of the body. Catarrhal conditions are common. The mouth is often foul and the gums may show pyorrhea. The tongue may be somewhat swollen and is easily pitted by the teeth. Speech may be difficult, not only for this reason but because of the similar and coincident crippling of the laryngeal mechanism.

Bones and Muscles.—The bones fracture easily, and in younger subjects ossification is retarded. The muscles contract with less than normal vigor, and fatigue is soon complained of after exertion. In some cases of juvenile myxedema the neck muscles are too weak to support the head. In older patients muscular pains and cramps are everyday complaints, and may be the overshadowing clinical sign of the whole disorder.

Heart and Lungs.—The heart may be infiltrated like the subcutaneous tissues, and its action embarrassed. The pulse is slow and blood-pressure low. The temperature is apt to be moderately subnormal throughout the day. Respiration is slowed, and dyspnea abnormally increased after exertion. Pulmonary infections are borne badly. Pulmonary tuberculosis is a common complication.

Stomach and Bowels.—The appetite is poor. It is hard to persuade hypothyroid patients to drink water. Ordinarily there is marked constipation, or a constipation alternating with fermentative diarrhea. Appendicitis is said to be common.

The *liver* is large. Its increase in size, together with the general relaxation and thickening of the abdominal wall, and the distention of the bowels with gas, produces often a large and pendulous belly. Gall stones and catarrhal icterus are among the commonly mentioned complications.

Blood.—The blood shows anemia, a relative lymphocytosis and other signs of secondary trouble. There are no characteristic changes.

Sex Organs.—The changes are mostly those of functional depression. In children infantilism persists. In young women amenorrhea is to be expected, but is not always present. In women around the menopause there may be menorrhagia or irregular bleeding, but this is not always due to the myxedema. In both sexes sexual desire is reduced or absent.

Kidney and Bladder.—Care must be taken not to confuse the urinary findings of myxedema with preëxistent or accidentally concomitant states. Nephritis and diabetes are to be distinguished by their peculiar signs. Albuminuria is not a constant sign of myxedema, but a reduced nitrogen output is always to be expected.

Unless the patient can be persuaded to drink water freely, the quantity of urinary fluid is much reduced. Catarrhal cystitis is a frequent complication. In younger patients enuresis is to be expected.

Nervous System.—There is very generally a marked depression of mental activity, sometimes amounting to a complete change of temperament and disposition. The mental changes may be the most significant fact in the clinical picture of the disease. Processes of thought are slow and difficult, the memory is impaired, the sleep disturbed and the acuteness of the special senses dulled. The patient may have hallucinations of hearing and sight. He is often melancholy. He complains of headache, which may be worse in the morning and wear off in the course of the day He has a constant sense of fatigue, which like the headache is worse in morning. The unmanageableness of the muscles, already referred to, is the more embarrassing by reason of the sluggish will. Epilepsy and many forms of insanity are well known to be associated with deficient thyroid secretion, but from the numerous records of these cases it would appear that the thyroid depression is secondary. Thyroid medication may help, but does not cure.

Metabolism.—Finally it is to be noted that the basal metabolic rate is lowered. The lowering may be 20, 30, or even 50 per cent below the norm for the age and sex of the patient. One must, however, always remember that this lowering is clinically far from being a pathognomonic sign. There are many general wasting diseases without fever in which the basal metabolic rate is lowered as a secondary phenomenon.

Cachexia strumipriva, or *thyreopriva*, follows a thyroidectomy in which the gland was too thoroughly extirpated, or the parts left were unexpectedly inactive. The story of the identification of this disease is told on p. 44. In this country, as an operative result of thyroidectomy, myxedema is claimed by the surgeons to be extremely uncommon. Recent figures from the Lakeside Hospital in Cleveland gave it as occurring only once in 500 operations. Symptoms and signs are in a general way identical with those of ordinary myxedema or minor hyperthyroidism.

Diagnosis.—Typical and well-marked cases, with a thyroid struma or a scar in the neck and a history of operation, present but little difficulty. Milder forms, with only some of the symptoms, are sometimes perplexing. I once saw the typical waxy and puffy face, with swollen eye-lids and an ungainly fat body in a man, aged forty years, who visited my Clinic some years ago. He complained of constipation and cold extremities. When I told him he had myxedema, and ought to take thyroid gland, he laughed and said he "had taken a pound or more of that stuff" at other clinics, and had never gotten better on it; nor did he under my care. His physical examination was entirely negative.

Basal metabolic rate determinations are of value in doubtful cases; with the provisos already made large minus percentages are very significant.

In the Froelich syndrome (p. 190) developing in childhood the sex organs are undeveloped and the fat is increased, but the metabolic difficulty is mainly with the carbohydrates as far as is now known, and the mind may be normal or even unusually active. In adult years Froelich cases (men) have usually lost their sexual capacity, and females tell of "change of life" coming on in the late twenties or early thirties. But they retain most or all of their mental capacity, and I have known such women even in the sixties to be agreeable and alert talkers, and of excellent business sense. Pluriglandular cases, in which the thyroid appears to participate in the clinical syndrome, are discussed in Chapter XIV. When tetany or paralysis agitans is present it seems more reasonable to suppose that they are parathyroid complications (Chapter V), and not symptoms of myxedema.

When signs of myxedema are conflicting or deficient there is no objection to the therapeutic test (Section 2, p. 86).

Prognosis. No general statement can be made; the cases are all different. Many writers of fifteen and twenty years ago[1] were much more optimistic than physicians are today. The cases have been observed for longer periods, with less encouraging outcome. Bright's disease, diabetes, tetany and tuberculosis often complicate myxedema. They must, of course, modify the prognosis.

For uncomplicated cases coming on first in middle age treatment is in many ways very satisfactory; a partial recovery may be usually expected. I have noted elsewhere that thyroid cannot at present be given in any way so as to imitate perfectly the action of the patient's own gland. Cases where the patient's thyroid still has some surviving function are the most promising. Thyroid helps the crippled gland to do its own work more perfectly. Sometimes the reparative process seems to be almost complete, and medication may be stopped. In many other instances the extract must be indefinitely continued—always under medical supervision and on the general principle that frequent minimal doses best imitate Nature's own methods. In postoperative myxedema accessory thyroids may in time develop enough to bear the secretory burden.

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[1] Hertoghe: Loc. cit., p. 107 (and others).

The prognosis for growth in children is about the same as in cretinism; sometimes better, of course, when there is a recoverable remnant of gland still in the neck.

Treatment.—A thorough survey of all the pathological conditions and complications must first be made. Many general suggestions made under Graves's disease and cretinism (see previous pages) are applicable here. The bowels must be kept open, and the patient must be urged to drink water, hot, cold, mineral or carbonated, as preferred. Rest from labor is desirable, of course, and relief from mental distress of strain. The patient should be weighed twice a week. An initial loss of weight is a satisfactory indication that the mucoid infiltration is decreasing. The rules for thyroid medication are given in Section 6.

When diabetes or Bright's disease is present as a complication the diet must be appropriately modified. Insulin has the usual indications. In a simple case of myxedema in early years the daily ration should be in the standard proportion of 1 of fat, 1 of protein and 4 of carbohydrate. The food should be well selected and cooked and there should be an abundance of green vegetables to afford "roughage" for the sluggish bowels. Hertoghe[1] advises limitation of sugar.

5. MINOR THYROID TROUBLES.

Minor Hyperthyroidism.—This condition is believed to appear sometimes as a clinical syndrome in boys and girls between five years and the beginning of puberty. Holt and Howland[2] describe it as a condition marked by a rapid heart, tremulousness of the muscles, nervous and mental excitement and irritability, and an enlarged thyroid gland. The eyes are not prominent.

The duration of the disease is variable.

Treatment.—Treatment as suggested by these authors is purely hygienic. Cases extending through puberty may later develop into exophthalmic goitre, but recovery without complications is the usual rule.

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[1] Die Rolle der Schilddrüse bei Stillstand des Wachsthums, etc.; translated by Spiegelberg, München, 1900.

[2] Diseases of Infancy and Childhood, 8th ed., New York, Appleton, 1922.

Minor Hypothyroidism.—While this condition passes, of course, by imperceptible degrees into major thyroid deficiencies, yet it is of such clinical importance as to justify consideration in a separate section.

Age, Sex, Distribution.—All ages and both sexes are affected, and its distribution is coëxtensive with that of the human race on this planet. It affects all social classes. It occurs as a temporary or a relatively permanent condition. Some authors think it more prevalent in colder climates. I do not know whether this can be verified or not.

Causes.—Causes are various. Any kind of tumor of the thyroid (with the obvious exception of the primary epithelial hyperplasias) may conceivably injure the secretory epithelium of the gland or compress or destroy the nutrient vessels. A large cyst may occlude the nearby vessels by compression. In long-standing cases of Graves's disease the condition is sometimes a terminal one. As a result of thyroidectomy it is also an occasional occurrence. But incidentally it must be also be remarked that by thyroid operations of other kinds, especially the removal of cysts and encapsulated tumors, thyroid insufficiency may be sometimes cured, the tumor removed being merely the mechanical cause of dysfunction.

There are some occupations, such as that of the glass-blower and the player upon wind instruments of music, which are said to interfere with the circulation in the neck, and predispose to thyroid dysfunction. Many minor chemical and circulatory disturbances not shown by the microscope are nevertheless capable of producing a distinct hypothyroidism. The neck may show nothing amiss, and the roentgen-ray shadow of the gland be of good size, and still a functional incompetence manifests itself by plain general signs.

Symptoms.—1. *In Children.*—The symptoms are often perplexing. The thyroid is, of course, secondarily affected by wasting diseases, such as chronic indigestion and marasmus. Giving thyroid to these babies, however, will do no special good. If the general nutrition is improved by diet, hygiene, sunlight and the proper vitamins, the thyroid takes care of itself.

The state of the teeth is an important sign. When an apparently healthy and well-fed child shows great retardation in the eruption of the milk teeth, thyroid lack is to be suspected. I have seen half a dozen teeth sprout in the toothless gums of such an infant within two weeks after thyroid was given. Healthy babies (especially girls) are at times born with two or more teeth. But regularly the two lower middle incisors appear during or at the end of the seventh, and the two upper middle incisors at the end of the eight or ninth month after birth. When a baby a year old, with no apparent general disease, still has no teeth, a minor grade of hypothyroidism may be suspected.

A lack of cheerfulness, of smiling response to friendly overtures when the time first comes (a few weeks to two months) for such demonstrations, may be a suggestive sign. General developmental retardation (a "justo-minor" state) is possible of course, but not so common. In slightly hypothyroid babies one never sees myxoid swelling of the subcutaneous tissues, but chronic eczema, milk crust or urticaria may be very obstinate. In some cases the hands are pudgy, the fingers stumpy and the grasp uncertain. The skin is not always dry nor the hair and nails brittle. These organs may be perfect. While a reduced rectal temperature, cold hands and feet and troublesome constipation are text-book signs, it is surprising how often they are absent. After the twentieth month gaping fontanelles may be significant, but rickets and hydrocephalus are also common causes of delayed cranial ossification. Even the mentality may not be greatly retarded—as Emmett Holt remarked a great while ago—and the diagnosis must be based on the impression made by the symptom complex. While such patients are especially prone to the catarrhal inflammations of childhood, the tendency is far from being pathognomonic.

Enuresis nocturna in older children has been thought to be due in many instances to hypothyroidism. The literature of fifteen years ago contained many references to this question. Hertoghe[1] reported instances of the apparent cure of enuresis by thyroid. Leonard Williams[2] also quoted a series of cases, a large majority of which were greatly improved by thyroid medication. But enuresis is often attributable to other causes as well. Some of the cases are even harmed by thyroid.

Now and then there are cases of hypothyroidism in small children in which the diagnosis cannot be made except by a cautious tryout of the extract.

2. *In adults* minor hypothyroidism has no consistently or persistently reliable signs. A thyroid tumor, or the scar of a former thyroidectomy, will naturally turn one's thoughts to such a diagnosis; but with such tumors and scars normal function is common enough probably the rule rather than the exception. A subnormal temperature, cold hands and feet, sluggish bowels, a rough

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[1] Bull. de l'acad. de méd. de Belgique, 4. ser., **21**, No. 267.

[2] Lancet, May 1, 1909.

skin, mental dulness, loss of energy, a failing memory, a constant sense of fatigue and discouragement, irregularly distributed pains and aches in the muscles and fasciæ—these are the so-called classical symptoms. Yet any well-trained physician can mention a half dozen other diseases in which more than one of these symptoms occur.

Finally must be mentioned the slowed-up metabolism, which may be reduced from 15 to 40 per cent. As elsewhere explained at length, this sign may be of great value, both positively and negatively; but it is only a confirmatory sign and always to be controlled by other manifestations.

Diagnosis.—The diagnosis can, therefore, often be made only after prolonged study of the case, and application of the information afforded by laboratory aids. Some cases cannot be definitely identified except by the therapeutic test.

Prognosis.—The prognosis is remarkably good. No thyroid troubles of any kind are so easily and completely repaired. Unless the cause is irremovable, thyroid therapy registers successes in more than 90 per cent of the cases. Except perhaps in the case of digitalis in auricular fibrillation, I know of no disease where the accurate adjustment of the remedy to the trouble evokes more surprise and gratification on the part of the patient.

Treatment.—Treatment consists in the removal of such causes as can be found, the care of evident complications, and the giving of thyroid (see Section 6 for therapeutic details). When tumors of the thyroid are present, such as small cysts, encapsulated adenomata, fibroid masses, early operation is the safest method of cure. After operation the gland often rebounds promptly into its normal condition. When operation is refused, or for various reasons is to be postponed, giving thyroid in suitable doses relieves the symptoms of thyroid deficiency, and for a time may even arrest the growth of the tumor. I have frequently seen small cysts grow smaller after thyroid medication. But such a procedure is not the first thing to be recommended.

6. THERAPEUTICS AND ADMINISTRATION OF THYROID GLAND.

In order to understand fully what the thyroid therapeutic problem comprises, one may perhaps with advantage subdivide the subject a little, and consider in succession the sources of raw material, the processes of preparation, the contraindications and indications for treatment, and the details of bedside administration.

Sources of Raw Material.—As to the sources of raw material, sheep glands, being large and easy to get at, were once popular. Presently, however, someone discovered that they owe their size often to cystic and fibrous degeneration, and that instead of being a safe reliance they are often inert, and as claimed by some, even toxic. After the researches of Baumann[1] indicated that iodine was the important constituent in the gland, and when the working-out of an easy and practical quantitative test for organically combined iodine by Riggs and A. Hunter[2] had simplified the chemical technique it became practicable to assay the iodine in thyroid tissue, and make the iodine percentage the basis of standardization.

In answer to the practical question, What glands contain most iodine? the work of Hunt and Seidell has become classic. Hunt's list of the iodine percentages in the thyroid of common mammals is to be found on p. 47 with comments. From Hunt's table the conclusion has been drawn that pig's gland is the best for therapeutic purposes. Many specialists write for this gland exclusively nowadays, and most manufacturers use it. It must not be forgotten, however, that bullock's gland comes nearest to the human percentage. I am also told by the veterinarians generally, and the statement seems to be borne out by Sisson's classic work on veterinary anatomy,[3] that bulk for bulk the bullock's thyroid is smaller than that of any other commonly available domestic animal. Both its density and its iodine percentage are points favoring its therapeutic use; and as far as my personal experience goes, I have found it very satisfactory. Probably no one will question that the worst extract of all for therapeutic purposes is that from the thyroid of the dog. This gland is not only scanty in iodine, as already mentioned, but in its action on other animals it is remarkably toxic. I have seen a sheep lose half its weight and become desperately ill with diarrhea, fever and tremor from one large subcutaneous dose per week of saline suspension of dog's thyroid for three weeks.

I have already noted the curious fact (p. 47) that all raw thyroid is richer in iodine in summer than in winter. One New York specialist that I know emphasizes this fact, and to certain of his patients gives only summer-gathered glands. Personally, I have never been able to see any difference so long as the gland after drying is standardized to a given iodine percentage. S. P. Beebe[1] recommends the therapeutic use of human gland.

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[1] Loc. cit., p. 46.
[2] Lóc. cit., p. 47.
[3] Loc. cit., p. 273.

The U. S. P. IX (1916) standard for desiccated thyroid is as follows:

"Thyroideum Siccum.
"Dried Thyroids.
"Thyroid. Sicc.

"The thyroid glands of animals which are used for food by man, freed from connective tissue and fat, dried and powdered, and containing not less than 0.17 per cent, nor more than 0.23 per cent, of iodine in thyroid combination. One part of dried thyroid corresponds to approximately 5 parts of fresh glands.

"A yellow amorphous powder having a slight characteristic odor. Dried thyroid must be free from iodine in inorganic or any other form of combination than that peculiar to the thyroid. Dried thyroid contains not more than 6 per cent of moisture and the yield of ash does not exceed 5 per cent."

The Tenth Decennial Revision of the U. S. P. (1926) makes a few verbal changes in the descriptive matter, and drops "Siccum" from the official designation. Dry thyroid extract is to be called Thyroideum (Latin), Thyroid (English), and the official abbreviation is *Thyroid.* for either language.

The adoption of the iodine standard was largely due to the enlightened views and scientific labors of Hunt and Seidell. Dr. Hunt's own account of the matter deserves to be recorded permanently.[2]

"Seidell and I continued our studies on thyroid as a drug, and as a result of the examination of a large number of samples on the American market made exact recommendations for a U. S. P. Standard, not only as regards iodine percentage, but as to the method for determining it, suggested standards for ash and moisture content, etc. These standards were adopted in their entirety by the Pharmacopœia Revision Committee, and Dr. Seidell was asked to prepare the pharmacopœial test. How important it was to have such a standard may be judged from the fact that we had found the iodine percentage in some of the tablets most widely used at that time to vary from 0.084 to 0.32, and the physiological activity to vary accordingly; we had remarked that 'The use of such preparations would seem as illogical as would that of preparations of Fowler's solution showing variations of 400 per cent in arsenic content.' Later we found thyroid samples which ranged from 0.02 to 0.5 per cent; the latter showed about 25 times the physiological activity of the former. . . . I have given this history in some detail, for totally erroneous accounts have been published as to the circumstances leading to the adoption of the U. S. P. Standard for thyroid."

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[1] New York Med. Jour., 1916, **104**, 445.

[2] Am. Jour. Physiol., 1922–1923, **63**, 257.

Preparation of Raw Material.—Passing to the preparation of raw material, there is only space to say briefly that most American wholesalers and manufacturers buy their raw material nowadays in bulk, frozen, from the Chicago and Kansas City meat packers. Personally, I doubt the advisability of this. One cannot be sure that autolysis does not take place, even when the glands are well frozen; and when the freezing mechanism goes awry (as it does), decomposition proceeds with the greatest speed.

The drying, too, is often done too slowly, and at too high a temperature. Furthermore, nearly all the commercial chemists emphasize the removal of fat (with acetone or some other fat solvent) from the crude gland; but the fat solvent is apt to dissolve or destroy also some of the active parenchyma of the thyroid cells. At my instance several New York dealers are now selling thyroid tablets made without fat extraction and without freezing. Perfectly fresh glands are worked up in suitable lots each day, and the tablets are ready for prescription six hours after the animal has been killed. These tablets are efficient in extremely small doses, and toxic effects are very rare.

The dry whole gland, of suitable iodine content, is still the most popular thyroid medicament. Some clinicians ascribe peculiar virtues to globulin, nucleoprotein and lipoid extracts. Kendall's thyroxin[1] is a definite chemical compound which contains 65 per cent of organically combined iodine. It is especially useful when the dose has to be given intravenously. Whether it has all the efficiency of whole dry thyroid has been already discussed. No one has claimed greater efficiency for dry thyroid except Hunt in the acetonitrile test in mice. Thyroxin (Latin *Thyroxinum*, abbreviation *Thyrox.*) is official in the Tenth Decennial Revision of the U. S. P.

From the exhaustive chemical researches of to-day it seems a "far call" to the days I recently heard recalled by an elderly neurologist at a medical meeting in New York. His messenger went every day to the abattoir and brought fresh thyroid (probably sheep's) which was minced in the doctor's office and fed to the patients in sandwich form.

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[1] Loc. cit., p. 48.

Administration, Bedside Details, Indications and Contraindications.—Having successfully made the diagnosis of cretinism, or myxedema, the young student recalls to himself the wonderful illustrations in the text-books of the "befores" and "afters," and fancies that his own results will be even finer. But certainly so far as my own experience goes, these people are a very disappointing class of patients. Thyroid cannot be given, either by mouth or vein, in such a way as to imitate perfectly the performance of the patient's absent gland. He improves; he never gets well. Even when a cretin baby has for some years progressed so wonderfully that the ladies in his mother's parlor say they cannot distinguish him from a perfectly normal boy, the other boys at school will find him out the very day he is enrolled, and with the atrocious cruelty of the wolf pack they will make his life a bitter experience for him.

We must regretfully school ourselves to the conviction that our greatest successes will be among patients—all ages—with minor deficiencies. Here there is still some normal gland at work; help from outside will act as a crutch for the limping organ until it can gather its normal activities together again and "go it alone."

Another fact must always be borne in mind, that thyroid by mouth is not always well absorbed. Much of it, and unfortunately a variable amount from day to day, may pass out with the stool, unabsorbed, or somehow otherwise remain inert. There is not then any great advantage in dogmatically stating maximum and minimum doses. In a general way $\frac{1}{4}$ gr. to 10 gr. of the ordinary commercial extracts may be needed at a single dose. The special preparation which I have noted above, and which I very generally use, acts quickly and well in doses of $\frac{1}{4}$ to $\frac{1}{2}$ gr. several times a day. It is rarely toxic in any ordinary dose. One patient, aged fifty-five years, recently in my care, misunderstood her directions, and instead of three took nine tablets per day, reporting two weeks later that she felt a great deal better.

One should, of course, keep a watchful eye upon the percentage of iodine, but of several commercial extracts of the same iodine content (at least so marked on the package) one may be much more toxic than another. Small doses frequently repeated are best, and the total quantity per day should be slowly increased until clinical effects begin to appear or toxic symptoms are noted. Common toxic symptoms are *nausea, vomiting, diarrhea, fever, excitement, rapid pulse, insomnia, rapid loss of weight,* and *a fine muscular* *tremor* or even *tonic spasms.* This condition is sometimes called "thyroidism." McCarrison notes that thyroid in excessive doses will also produce or aggravate enuresis in cretin or hypothyroid children.

When thyroid is given for the first time to a cretin (or a patient with myxedema) a loss of weight is apt to occur. This seems due to the disappearance from the tissues of the "mucous" edema described fully in the appropriate section, and to the oxidation of excessive fat. Conceivably the effect of such a process on the heart might be temporarily to weaken it, and it is recommended to keep the severer cases in bed when this is feared. McCarrison thinks, also, that small children beginning to improve under the treatment should not be encouraged to stand or walk until the bones are strong enough not to bend.

Leonard Williams[1] affirms that one valuable sign of "thyroidism" in children is a sudden and profuse nasal catarrh. I have not myself observed it. McCarrison speaks of subthyroidic patients whose hair falls "in handfuls" on first taking thyroid. But this is only to make room for a far better growth.

The dose of Kendall's thyroxin by mouth is 0.2 to 0.8 mg. Of crystalline thyroxin by vein the dose is 1 to 10 mg. Thyroxin is marketed only by E. R. Squibb's Sons, under license of the University of Minnesota. The oral dose may be repeated several times a day, as required. The intravenous injection should be given only every ten days or two weeks. The solution should be prepared *ex tempore* by dissolving the desired amount of crystalline material in a little sodium hydrate solution in a sterilized test-tube, and standing the test-tube in boiling water for five minutes. Full directions accompany the package. A package of 10 mg. (pure crystals) now retails at $3; but the expense is not so great as might appear when the long interval between doses is recalled. At the Mayo Clinic it is recommended to give oral thyroxin (each dose) with a little bicarbonate of soda, to avoid disturbance of digestion.

Whatever be the preparation used, the attending physician should remember that he is using an edged tool; each case requires accurate individual study from day to day and from week to week. Toxic symptoms may develop unexpectedly. The dose should be reduced in hot weather and occasional complete intermissions are desirable.

Indications for thyroid therapy are in general coëxtensive with the clinical indications of hypothyroidism, using that word in the widest physiological sense. Within the clinical limitations already noted (p. 39), a well-marked minus basal metabolic rate is an indication for giving thyroid.

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[1] Brit. Jour. Child. Dis., June, 1909.

The use of thyroid gland in *obesity* is considered also in Chapter XV.

A few apparently non-specified therapeutic uses of thyroid gland must be also mentioned. I say "apparently non-specific," for a closer study of the basal metabolic rate in the cases may in the future show that the successes are confined to patients with minor hypothyroidism. This can at present be only suspected. But it is true, for example, of certain cases of troublesome *muscular rheumatism* that, however carefully they are studied by modern methods and treated with all varieties of salicyl derivatives, they will not get well until thyroid is given. While on general principles it is advisable to give thyroid only after a basal metabolic rate test has been made, this may not always be practicable, for a variety of obvious reasons. In such circumstances minute doses of thyroid may be tentatively given, and the case carefully watched. The literature contains numerous references to the beneficial results that may be got by the thyroid treatment of myalgia. Far more astonishing, but unfortunately far less frequent, is the benefit that results now and then from thyroid in the most difficult and disheartening cases of *arthritis deformans*. One should never omit (when it is possible) to test the basal metabolic rate in these cases in the hope that thyroid therapeusis may be of at least some temporary value.

Thyroid has also some claim to useful effects in such diseases of the bones as ununited fractures and osteomalacia; in certain definite skin diseases, like *psoriasis* (McCarrison warns that in *excessive doses* it may make psoriasis much worse) and in many indefinite skin affections, of which itching is the common character. It has been also recommended in hay fever, in asthma, in cancer, in hemophilia, but with far less consensus of opinion as the benefit derived from its use.

There are some cases of *menorrhagia* that seem to be much benefited by thyroid extract.

Contraindications.—Thyroid gland is contraindicated in all cases of exophthalmic goitre. No patient even suspected of this disease should receive this remedy. In dangerous and violent phases of the disease thyroid may precipitate a fatal result.

In a more general way the caution should be noted that there are many cases of apparently benign goitre or benign adenoma in which the careless administration of thyroid induces or reinforces the appearance of the Graves syndrome. It is safer in these cases to give iodine only (as elsewhere described, p. 62), and even iodine must be carefully watched.

In "spent" cases of Graves's disease, of some years' duration, when the metabolism is subnormal and the case has become really one of hypothyroidism, thyroid may be tried, always with great circumspection and constant supervision. Should the patient be going on a journey or be living at a distance, full explanations should be made of the action of the medicine and the signals for its withdrawal.

A day or one-half a day before thyroidectomy upon cases of Graves's disease it is recommended by some surgeons as a routine practice to give at a proper interval two or three average doses of thyroid extract to the patient, the object being to avoid a too sudden withdrawal of the source of supply. The amounts and intervals depend on the particular case. The effect of the dose would ordinarily not manifest itself until after the operation. This is obviously not giving thyroid to relieve the Graves symptoms.

In paralysis agitans C. L. Dana remarked many years ago that thyroid always does harm.

Whenever possible, in hypothyroid conditions of every degree, it is the ideal method to control the action of the thyroid extract by periodic tests of the basal metabolic rate. Successive tests in the same person, as has been already noted, are more accurately comparable with one another and of greater clinical value than single tests on different individuals. In small children the test is impracticable, and the clinical signs are the only guide.

CHAPTER V.

THE PARATHYROID GLANDS.

Historical.—The parathyroid glands were discovered by Ivar Sandström.[1] His account is very complete, embracing the dog, cat, bullock, horse and rabbit (outer gland only) as well as man. He proposed the name *Glandulæ parathyreoideæ.* Microscopically he noted that the parathyroids are entirely distinct from the thyroid; and he comments that Remak, in 1858, and Virchow had undoubtedly noticed these bodies and speculated as to their function. A. Kohn[2] verified Sandström's work, commented on the embryology of the parathyroids, amplified the previous descriptions, confirmed the identity and independence of the glands, and described their position in rabbits and cats. He describes very plainly the "internal parathyroid" of rabbits as buried in the lateral lobe of the thyroid. E. A. Gley in a succession of short *communiqués*[3] announced and amplified the important discovery that removal of the parathyroids causes fatal tetany, and that this symptom complex is entirely independent of any influence that the thyroid may exercise. Gley's discovery was rapidly followed by a succession of papers on the same subject. Some years later Ochsner and Thompson[4] in a thoughtful and extensive review of the subject to that date listed nearly 200 titles, and the literature since that time is still larger. H. Bergstrand[5] gives more than ten closely printed pages of references, and even these lists are quite incomplete.

Name.—The name these glands generally go by today is still Sandström's original name. No other name has had much vogue except the German terms, *Epithelkörperchen* (from the microscopical appearances of sections) and *Nebenschilddrüsen.* The general English and American usage is *parathyroid glands.* N. W. Janney[6] thinks Dock's adoption from Verdun of the term *branchial glands* would be fortunate.

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[1] Schmidt's Jahrbücher, 1880, **187**, 114; abstracted from Upsala Läkaref. Förh., 1880, **15**.

[2] Arch. f. microscop. Anat., 1895, **44**, 366, and later papers.

[3] Compt. rend. soc. de biol., 1891 to 1897.

[4] Diseases of the Thyroid and Parathyroid Glands, St. Louis, Mosby, 1910.

[5] Acta Med. Scandin., 1919–1920, **52**, 791.

[6] Abt's Pediatrics, Philadelphia, Saunders, 1924, vol. **4**.

ANATOMY.

Number of Glands.—The parathyroid glands are usually four in number. The writer[1] summarized the results of 130 autopsies, finding sometimes only two or three, several times five, once six, generally four.

Variations in the number of glands have had a curious interest for physiologists. Exact methods of research are necessary to avoid error. H. Petersen advises as follows[2] when removing the glands at autopsy: With a long knife cut away, *in toto*, from below, through the thoracic inlet, the wind-pipe, gullet, thyroid, larynx and tongue, working carefully up against the cervical spine so as to remove the entire contents of the front of the neck between the skin and backbone. Lay the mass thus obtained on a board—thyroid down and gullet up—and traverse the whole mass with forceps and scalpel. Everything is to be put by that looks suspicious. The microscope must be used for doubtful objects. Bits of fat and thymus, small lymph nodes, hemolymph nodes and accessory thyroids confuse the beginner. Experience largely overcomes these difficulties.

R. L. Thompson[3] notes that where only three glands could be found by dissection he was often able to find a fourth by putting the neck organs in Pick's solution and subsequently developing the tissue in 80 per cent alcohol. In case of edema and congestion 10 per cent of formalin solution was also helpful in showing up glandules overlooked in fresh material.

Allowing for oversights and special difficulties, it may be safely said that there is no special magic about the number four. Five glands (two on one side, three on the other), six glands, eight glands, one gland—have all been reported, and it is quite possible that one large one alone can function for the entire human economy. But at least one parathyroid is always present. There seems no longer any question of this. The burden of proof has been shifted to those who deny it.

Accessory Parathyroids.—Accessory parathyroids are also found, but there is no record (that I know of) of this occurrence except somewhere in the front of the neck. A. Pepere[4] and R. L. Thompson[5] have described accessory parathyroids. Pepere distinguishes between accessory *glandules* and accessory *islets,* the latter being discoverable only in serial sections of other tissues in the neighborhood of the thyroid, such as fat, cellular tissue and thymus nodes.

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[1] Presbyterian Hospital Reports, New York, 1906.

[2] Virchow's Arch. f. path. Anat., 1903, **174**, 3.

[3] Ochsner and Thompson: Loc. cit., p. 118.

[4] Le ghiandole paratiroidee, Torino, 1906; Trattato di anatomia patologica. Torino, 1922, **8**, 66; literature.

[5] Loc. cit., p. 118.

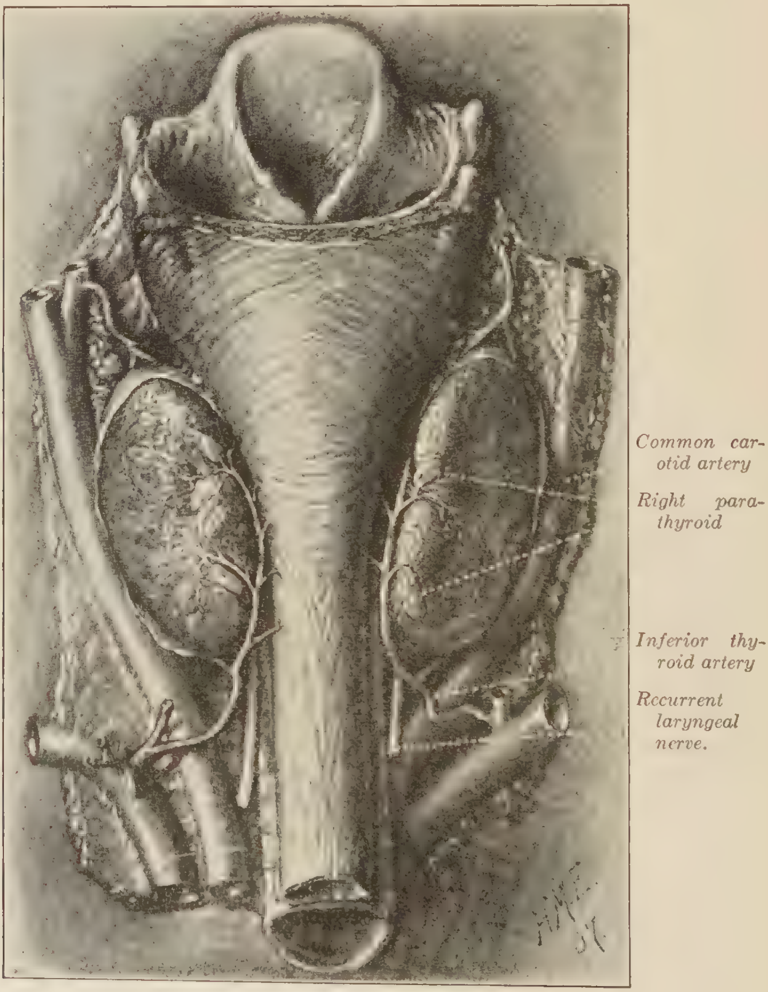

FIG. 26.—Dissection of parathyroid glands. (Halsted and Evans.)

Macroscopical Appearances.—H. Bergstrand[1] gives a recent elaborate description of the gross and minute anatomy. The writer, in 1906,[1] gave the following description: The average gland is about as large as a small grain of maize, 6 by 4 by 2 mm. It is usually flattened like a melon seed, but may be ovoid or spherical. It is softer than a lymph node of the same size, reddish-yellow or brownish-yellow in color, and has a thin fibrous capsule with characteristic venous tracery. The maximum weight of four glands from one subject (a woman, aged sixty-four years) was 0.376 gm. The glands usually are above and below the middle point of the rear border of the thyroid lobes, and are apt to fit into notches on the edge of the larger gland (Fig. 26). The upper left gland is often higher and deeper than the upper right. One or more glands are said to be sometimes found 2 inches lower than the thyroid in the neck or even imbedded in the thyroid glands. I never noticed such positions in the human subject, but every now and then the glands may be doubled and separate, or doubled and connected by an isthmus.

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[1] Le ghiandole paratiroidee, Torino, 1906; Trattato di anatomia patologica. Torino, 1922, **8**, 66; literature.

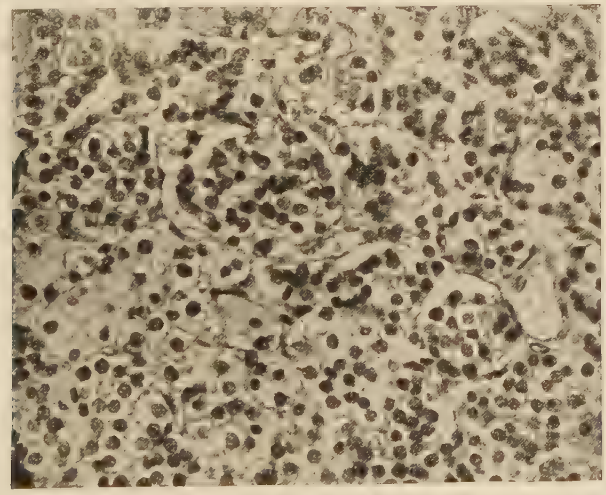

Fig. 27.—Section of human parathyroid. × 400. (Sharpey Schæfer. Photographed from a preparation by M. Kojima.)

Histology.—The fine structure of the parathyroid is characteristic in all mammals and can be recognized readily after the necessary experience (Fig. 27). The arrangement of the secreting cells is very similar in a general way to that of the pituitary (pars anterior) or the adrenal cortex. The cells are grouped in solid anastomosing columns supported by loose and often fatty connective tissue. The minute appearances of the cellular protoplasm have been differentiated by numerous writers, and a small volume might be compiled on this subject alone.[1] Ochsner and Thompson,[2] after a review of the literature, think it correct to distinguish between *principal cells*, which make up most of the total, and scattered groups of larger cells with small deeply staining nuclei and a relatively large amount of granular, eosinophile cytoplasm. The weight of opinion inclines to the conclusion that these differences are due only to different physiological states of rest and activity. The cells are occasionally grouped around what appears to be a small lumen containing a structureless "colloid" supposed to be cell secretion. The same "colloid" may be noted in small vessels throughout and around the glands. The connective tissue is of variable quantity and density. The fatty tissue is often very abundant, both around and among the cellular trabeculæ.

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[1] Loc. cit., p. 119.

The *vessels* of the parathyroid glands are derived from the superior and inferior thyroid systems. The veins seem to contain valves rather frequently. The lymphatics present no special features. Thompson found that ligating the largest artery to a dog's parathyroid seemed not to affect its function or structure, the presumption being that collateral circulation is good.

The *nerves* to the parathyroids have also been studied. The sympathetic twigs to the thyroid seem to send accessory branches to the parathyroids.

Embryology.—The embryology of the glands throws no light on their function. The text-books on anatomy may be consulted for details. C. E. Benjamin[3] derives them from epithelial "Anlagen" originating in the third and fourth branchial clefts. He also gives a review to date of literature on parathyroid development.

THE CHEMISTRY OF THE PARATHYROID GLANDS.

The chemistry of the parathyroids has been disputed. Gley affirmed the presence of iodine in them. With the improvement in methods of analysis since that author's work, his conclusions have been generally denied. No specific chemical reactions of the parathyroid glands have been discovered. No active principle has been isolated. Extraction methods for physiological experiments and for clinical purposes are described later. Proteins are abundant. Nucleoproteins and globulins may be separated in the usual way. Albumins are also present, and an abundance of mucinoid bodies. These probably come more largely from the connective tissues. The new work of J. B. Collip is mentioned on page 131.

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[1] For literature see Bergstrand (Loc. cit., p. 118).

[2] Loc. cit., p. 118.

[3] Ziegler's Beiträge, 1902, **31**, 143.

THE PARATHYROIDS IN INFANTS.

The parathyroids in infants present unusual difficulties, taxing all the resources of the pathologist. In new-born infants it is well to harden the entire neck in formaldehyde before beginning dissection. Several dozen small objects no bigger than bird shot or grains of sand have to be considered, and very generally the microscopical examination of serial sections is the best resort. The same method may be followed in the study of fetal parathyroids. I have had very good success with it.

THE PARATHYROIDS IN OTHER ANIMALS.

The zeal and thoroughness with which the students of physiology and comparative anatomy have attacked this topic is really quite notable. D. Forsyth[1] published an extended account of the situation of the parathyroids in mammals and birds. Guleke[2] gives six pages to the subject, with references, considering the dog, cat, rabbit, bat, Didelphys (opossum), goat, sheep and adding some notes on reptiles and fishes. W. L. Estes[3] studied the glands of the horse, finding two in addition to the two described in the original account of Sandström. Gley, Kohn, MacCallum, Thompson and Leighton, Alquier and other observers have made notes on the conditions in the common domestic animals. There is only space in this volume to note such facts as may be of value in ordinary laboratory work.

Dog.—Some comments have been made already on page 42. The dog's parathyroids are usually four, two on a side. They lie without any great regularity on or under the capsule of the thyroid lobe of the same side. Exceptionally one or more of them may be imbedded in the thyroid or of such small size as to be virtually invisible. Accessory parathyroids in this animal have also been described by several observers. One cannot, therefore, expect 100 per cent of successful parathyroidectomies in dogs, but as the large thyroid lobes are readily compensated for by accessory thyroids, uncomplicated parathyroid tetany will very generally ensue after removing the thyroids and parathyroids together. This is the usual laboratory operation on dogs to-day when tetany is to be produced. It is easily and quickly done, and the anesthetic recovered from in less than an hour.

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[1] Brit. Med. Jour., 1907.

[2] Loc. cit., p. 135.

[3] Bull. Johns Hopkins Hosp., 1907, **18**, 335.

Cat.—The parathyroids in this animal are also four as a rule, and they are commonly situated in positions resembling the dog's. Harvier and Morel[1] have described accessory parathyroids in the thymus of the cat in about one-half the cases. In a recent paper Nicholas and Swingle[2] describe accessory glands in 35 per cent of 62 cats operated on. This fact makes cats unsuitable subjects for laboratory experiment.

Rabbit.—The thyroid has a thin isthmus. There are four parathyroids. Two are below and exterior to the thyroid. Two are imbedded in the lower outer thirds of the thyroid lobes. Operations on this animal are specially difficult, owing to the danger of cutting the recurrent laryngeal nerve, when the proper amount of thyroid is removed.

Ox.—The parathyroids in the ox are said to be four in number. The outer glands lie above and behind the upper pole of the thyroid of the same side, and are often half imbedded in a small mass of thymus. The inner glands are said to be buried in the thyroid. About 1 per cent of external ox parathyroids are cystic. Of accessory glands but little is known.

Monkey.—The thyroid may or may not have an isthmus. The parathyroids are four. Vincent and Jolly[3] report that both the parathyroids are often buried in the thyroid, making a simple parathyroidectomy very difficult or impossible. Horsley's good fortune with these animals has already been commented on.

Rat.—J. Erdheim's studies[4] indicate that two parathyroids are usually present in the rat, imbedded toward the anterior ends of the thyroid lobes. Accessory glands are variably present in the upper poles of the thymus on each side.

PHYSIOLOGY OF THE PARATHYROID GLANDS.

When a partial parathyroidectomy is done upon a suitable animal without injury to the structure or the blood supply of the gland or glands remaining, the subject recovers promptly, the wound heals, and no nervous or metabolic phenomena, either immediate or remote, are observed. When all the parathyroids are removed, either at one or at successive operations, a typical train of symptoms and signs supervenes. The animal recovers from the anesthetic, and for a few hours—perhaps for a day or so—eats and sleeps as usual, but presently sickens. The earliest and most notable sign is increase of muscular rigidity, with fine tremors of all the voluntary muscles. Voluntary control of muscular movement is interfered with. Dogs stagger; rabbits hop awkwardly a few times and then fall; cats walk irregularly, appear cross-eyed (spastic membrana nictitans—"tetany eye sign" of Nicholas and Swingle) and lift one foot now and then with a shake as though they had stepped in water ("wet-foot"). Rabbits often shiver as though with cold. This condition is accompanied in some animals with intermittent general convulsions. Convulsions in my experience are more apt to occur in young subjects, and death may occur during a convulsive attack. The animal languishes and may lie profoundly depressed and stuporous in later stages, but the tremor generally continues. Rabbits drool constantly. Intermittent salivation is noticeable in most experimental animals. The heart beats at an enormously rapid rate. Respiration is also hurried, and dyspnea is much increased by exercise. Dogs have marked trismus of the jaws at times. There are not many notes on the temperature of experimental animals; a few cases have been said to have fever. Transient albuminuria has been described. The animals generally refuse food, waste rapidly and if not carried off in a convulsion die in stupor. Herbivora and carnivora are alike affected. Cabbage-fed rabbits are even more violently ill than meat-fed dogs. Preliminary fasting does not in my experience materially delay appearance of symptoms. The duration of the condition is from a few hours to several days. In a few instances even several weeks have elapsed before death. In some instances animals desperately ill for half a day slowly recover and show no further symptoms. This result is probably due to the compensatory hypertrophy of a bit of gland left behind, or of an accessory gland not found.

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[1] Compt. rend. soc. de biol., 1909, **66**, 837.
[2] Am. Jour. Anat., 1924–1925, **34**, 469.
[3] Jour. Physiol., 1904, vol. **32**; 1906, vol. **34**.
[4] Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1906, **16**, 632.

J. Erdheim[1] has noted some anomalous effects in rats, indicating that the nutrition of the incisor teeth is impaired. Guleke,[2] after a study of the extensive literature, concludes that the growing dentine fails to calcify normally. The relation of the parathyroids to the formation of callus after bone fracture has been studied by many authors, mostly with negative results. A conservative recent review, with literature, is given by V. Ghiron.[3]

This train of symptoms goes by the name of *tetania parathyreopriva*, or in English *parathyroid tetany.* The phenomena have been observed in laboratories everywhere, and by operators of all degrees of experience and skill. A few negative and contradictory reports have been made—some of them by scientists of high standing, like Vincent and Jolly.[1] One is rather forced to believe that their selection of experimental animals (cats) must have been unlucky, or their experience of accessory glands unusual. L. R. Dragstedt's work is mentioned (p. 130) in another connection.

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[1] Loc. cit., p. 124.

[2] Loc. cit., p. 135.

[3] L'importanza delle paratiroidi secondo le odierne vedute, Roma, Pozzi, 1924.

Some laborious *metabolism studies* have been made upon parathyroid tetany. One of the most interesting is that relating to the blood sugar. Students interested in this special topic will find Watanabe's bibliography useful[2] for the earlier views. Hypoglycemia was once quite generally reported. But I. Greenwald[3] finds that after parathyroidectomy blood sugar is not reduced until tetany appears, when the increased muscular activity is sufficient to explain it. This is, of course, supplemented by the effects of starvation.

Physiological Chemistry.—The chemical problem presented by the facts just described has been attacked from various directions.

In 1902 J. Loeb and his pupils[4] had already called attention to the sedative action of calcium salts (in proper concentration) on nervous and muscular tissue, and these results were a little while later confirmed by Sabbatani[5] and other Italian students. Arnold Netter[6] reported 3 cases of infantile tetany cured, he believed, by oral administration of small doses (0.15 gm.) of calcium chloride. He also found it brilliantly successful sometimes in spasm of the glottis and in convulsions in infants.

In a little known Rumanian medical journal[7] C. Parhon and C. Urechie published accounts demonstrating beyond a doubt that intraperitoneal injection of 0.5 per cent calcium chloride in parathyroidectomized dogs relieved the tetany. This discovery was read before the French Congress of Alienists and Neurologists in August, 1907 (17th Session, Official Reports), and a summary appeared later.[8] A series of 20 dogs was used, and controls were made carefully at all points. Sodium salts were found to increase the violence of the spasms, and calcium had to be given in larger amounts in order to control the convulsive movements of dogs already injected with sodium.

In 1908 W. G. MacCallum and C. Voegtlin[9] made the same announcement independently, namely that *soluble calcium salts arrest the spasms of parathyroid tetany.* They therefore concluded that parathyroidectomy causes a *diabetes calcarius,* or calcium deficiency. The following year[1] they published a fuller account of their work, concluding that "Calcium salts have a moderating influence upon the nerve cells. The parathyroid secretion in some way controls the calcium exchange in the body. It may possibly be that in the absence of the parathyroid secretion substances arise which can combine with calcium, abstract it from the tissues and cause its excretion, and that the parathyroid secretion prevents the appearance of such bodies." They also reported analyses of the nervous tissues of a small series of dogs in tetany, finding diminished calcium; and they noticed an increase of calcium in the stools and urine of such animals.

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[1] Loc. cit., p. 124. [2] Jour. Biol. Chem., 1918, **33**, 253.

[3] Ibid., October, 1924, with recent references.

[4] References in paper by MacCallum (Loc. cit., p. 127).

[5] Riv. sper. di freniat., 1901, **27**, 946.

[6] Séances et mém. soc. de biol., 1907, **62**, 366.

[7] Revista stintelor medicala, July-August, 1907.

[8] Séances et mém. soc. de biol., 1908, **64**, 622.

[9] Bull. Johns Hopkins Hosp., March, 1908.

These authors also concluded from repeated experiments that "parathyroid tetany may be relieved by extensive bleeding with replacement of the blood by salt solution."

Berkeley and Beebe[2] in the same year reported a long series of parathyroid studies. They called attention to the apparent contradiction involved in the two statements of MacCallum and Voegtlin just quoted, the assumption being necessary that bleeding and saline infusion must diminish in much further degree the available supply of calcium in the subject animal, and ought therefore according to the first conclusion to increase the symptoms of tetany. Berkeley and Beebe verified the relief of tetany by bleeding and saline transfusion. They observed in further contravention of the calcium deficiency hypothesis that: (1) The symptoms of tetany are frankly those of a toxin acting on the central nervous system. (2) In diabetic acidosis there is a much increased excretion of calcium, in some instances amounting to 100 per cent more than by a normal person on the same diet, yet no tetany develops, though the acidosis may last for weeks. (3) That other metals belonging in the calcium group, not only magnesium as mentioned by MacCallum himself,[3] but strontium and barium, relieved parathyroid tetany; barium being poisonous could be used only with care and in small doses non-lethal to controls, but both barium and strontium salts when intravenously injected relieved parathyroid spasms almost as promptly as calcium. They suggested that all these metals in the circumstances act perhaps only symptomatically as nerve depressants. (4) That ammonia and xanthin convulsions in dogs are also promptly relieved by calcium and strontium injections. They conclude: "Without wishing to say that the various factors in the etiology of tetany are settled, we are disposed to think from the information now at hand that the parathyroids are chiefly concerned in furnishing enzymes which are of prime importance in the intermediary metabolism of nitrogen."

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[1] Jour. Exp. Med., 1909, vol. **11.**

[2] Jour. Med. Res., 1909, **20,** 149.

[3] Loc. cit.

Later studies have not been conclusive. For example, Jean V. Cooke[1] found that the calcium content of the blood of 2 dogs in tetany was actually higher than in 3 normal dogs, and a number of negative or discordant observations on calcium elimination in idiopathic tetany listed by Paton and Findley.[2] These authors verified the previous observations that bleeding and saline infusion abolish symptoms of tetany for the time. They remark (p. 332): "No doubt the proof of the relation of calcium to the onset of the symptoms is a matter of prime importance, and the content of the animal in available calcium at the time may play a part in the onset of the symptoms, whatever these symptoms are due to . . . The fundamental fact opposed to all such theories of calcium deficiency is the benefit produced by bleeding and the transfusion of saline solution."

It should be noted also that laboratory methods for the quantitative estimate of calcium require skill, and that the small amounts of blood, urine and feces usually selected for testing make minor errors in analysis bulk large in computing the final results. The entire subject of calcium metabolism in man and laboratory animals is at present in a grievous state of confusion, and the immense literature[3] is full of contradictions and deficiencies. It must be also remembered that there are many diseases without any known relation to parathyroid disease, like rickets and osteomalacia, in which the calcium metabolism is disturbed, and (as just noted) that in diabetic acidosis, for example, immense amounts of calcium are eliminated by the body for weeks at a time without the appearance of tetany.

Voegtlin and MacCallum later[4] somewhat modified their previously expressed views. They wrote: "We are probably dealing with a condition in which some poisonous material is developed in the course of metabolism. . . . Whether this poisonous substance acts by reducing the calcium content of the nerve cells seems still perfectly possible."

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[1] Jour. Exp. Med., 1910, **12**, 45.

[2] Loc. cit., p. 129.

[3] See review by H. W. C. Vines, Parathyroid Glands in Relation to Disease, London, E. Arnold & Co., 1924.

[4] Jour. Pharm. and Exp. Therap., 1910–1911, **2**, 447.

W. F. Koch in the following two years made an interesting further contribution[1] to the toxin theory. In dogs that showed definite parathyroid tetany he isolated a number of toxic bases, which he identified as choline, neurine, β-iminazolylethylamine (3 out of 5 dogs), and guanidine or methylguanidine (6 out of 6 dogs). From the urine of 1 dog he isolated (of the last-named substance) 1.9 gm. per liter of gold salt, an amount in great excess of previous records for normal animals. A. Biedl[2] had already tentatively suggested β-iminazolylethylamine as the toxin concerned.

Guanidine.—Guanidine, $HN:C(NH_2)_2$, an oxidation product of guanine, one of the group of purin bases, has been known for many years. Thorpe[3] ascribes its first identification to Strecker,[4] who produced it by oxidizing guanine with potassium chlorate and hydrochloric acid. It is said to be found normally in beet juices and bleached vetch seedlings. Small amounts of it in normal human urine were first reported (as methylguanidine) by Kutscher and Lohmann.[5] It is a deliquescent crystalline solid, soluble in alkalies and water, volatile, strongly alkaline, the thermal value of its basic function lying between barium hydroxide and sodium hydroxide. Boiling with baryta water or dilute sulphuric acid converts it into urea and ammonia.

The facts above mentioned, together with some observations by Pekelharing on the spastic influence of guanidine upon isolated muscle led D. Noel Paton and a group of his associates in the Department of Physiology of Glasgow University to investigate more fully its relation to parathyroid tetany, and the final publication fills more than half of vol. **10** (1916–1917) of the *Quarterly Journal of Experimental Physiology.*

Paton and his associates found guanidine or methylguanidine increased in the blood and urine of animals with tetany. By injecting normal animals with guanidine in suitable doses it was possible to produce many of the symptoms of parathyroid tetany. They claimed the similarity of the two conditions to be virtually an identity, and declared parathyroid tetany to be due to the appearance of guanidine in the blood of the parathyroidectomized animal.

Careful critical examination not of their conclusions but of their protocols is not entirely convincing. Animals poisoned with guanidine were not apparently promptly and entirely relieved by calcium injections. Klinger[1] thought symptoms of guanidine poisoning in cats strikingly like tetany, but calcium injections did not relieve them; and the cats showed appetite for food even after being poisoned for two or three days, which never occurred in tetany. Rats poisoned with guanidine behaved in an entirely different way from rats in tetany. Nicholas and Swingle[2] noted in cats that the symptoms of parathyroid tetany and of guanidine intoxication were markedly different. Watanabe[3] claimed that guanidine reduced blood sugar (p. 126), but he also was unable to relieve guanidine spasms with calcium injections.

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[1] Jour. Biol. Chem., 1912, **12**, 313; 1913, **15**, 42.

[2] Innere Sekretion, 2d ed., 1913, **1**, 125.

[3] Dictionary of Applied Chemistry, London, Longmans, 1922.

[4] Liebig's Annalen, 1861, p. 118.

[5] Ztschr. f. physiol. Chem., 1906, **49**, 81.

Gustav Bayer[4] found that rabbits, cats and guinea-pigs poisoned with guanidine showed a decrease in ionized calcium content of the blood in a few hours. On the contrary, Nelken[5] noted quite the opposite under what seemed to be similar conditions. To complete the confusion in respect of calcium in guanidine poisoning, Watanabe[6] reported some animals unchanged and some showing a decrease. Evidently from a series of reports like this nothing is to be inferred.

L. R. Dragstedt[7] concluded that the parathyroids are not essential to life, but that they prevent an intestinal intoxication, and that a proper diet (mostly milk) will enable animals to live indefinitely in perfect health after parathyroidectomy. But of his properly dieted subject animals, 6 puppies all died "suddenly" (as young animals generally do, in convulsions, at night?) within ten days after being operated on. Of 11 adult dogs in another group 7 died; of 15 dogs in a third group 10 showed transient tetany and 4 died. The development of accessory glands could account for the survivals and the calcium in the milk would be in itself lifesaving. Shapiro and Jaffe[8] have collated the evidence offered by Dragstedt, and by Luckhardt and Rosenblum, Luckhardt and Blumenstock, Luckhardt and Goldberg, and Dragstedt and Peacock, on the same subject, and have noted very correctly, I think, that careful feeding, nursing and medication merely tided the animals over the period needed for accessory glands to develop. They conclude: "No evidence has yet been presented that mammals can survive complete parathyroidectomy." The same comment may be made on the laborious monograph of H. A. Salvesen.[9]

[1] Arch. f. exp. Path. and Pharm., 1921, **90**, 129.

[2] Anat. Rec., 1924, **27**, 214.

[3] Jour. Biol. Chem., 1918, **33**, 231; **34**, 51, 65.

[4] Ztschr. f. d. ges. exp. Med., 1922, **27**, 119.

[5] Klin. Wchnschr., 1923, **2**, 261.

[6] Jour. Biol. Chem., 1918, **36**, 531.

[7] Jour. Am. Med. Assn., 1922, **79**, 1593.

[8] Endocrinology, 1923, **7**, 720, with references.

[9] Acta Med. Scandinavica, 1923, Supplement 6.

Vines,[1] who gives a valuable and extensive bibliography (without a single mistake!) has reviewed the recent literature, and seems much impressed by the cogency of the arguments for both sides of the parathyroid controversy. Like the Calvinistic theologian who affirms that "though God has predestined us, man is free," he states that the parathyroid has two secretions, and that one neutralizes a metabolic toxin (guanidine) and the other controls calcium metabolism. Nor is he without a "reason for the faith." He finds that he can, *in vitro,* cause the disappearance of a certain amount of guanidine by incubating it in acid solution for four days with a measured amount of parathyroid extract, and that in a series of patients with chronic ulceration (varicose ulcers, especially) a subnormal blood calcium percentage could be raised to normal by giving parathyroid, with coincident improvement or healing of the ulceration. He further suggests (with due scientific reserve) that by reason of their influence upon calcium metabolism the parathyroids are perhaps intimately concerned with the defensive mechanism of the body against bacterial toxins in general. These observations are thus far interesting speculations rather than demonstrations. They await confirmation.

W. G. MacCallum[2] reviews the later literature of tetany and reaffirms his previous conclusions. Professor Paton[3] also reviews the recent literature, and with great emphasis reaffirms *his* previous conclusions. I. Greenwald[4] concludes from a new series of chemical analyses that the analytical methods of Paton and his associates were inadequate for the identification of guanidine in blood and urine, and that there is no unusual amount of either guanidine or any other toxic substance in the blood and urine of dogs in tetany—only a deficiency of calcium.

J. B. Collip, and J. B. Collip and co-workers[5] announce that they have partly isolated from parathyroid gland a substance as powerful in its own way as insulin. The new extract (name "pending") when injected in suitable doses arrests tetany in experimental animals for a day or so, and causes a rise in the blood calcium. The chemical method of extraction appears essentially to be the concentration of an extract of fresh glands made by boiling in 5 per cent hydrochloric acid. Overdosing of dogs with this preparation, as these students report, caused an extreme rise in the calcium content of the blood (*hypercalcemia*), and long-continued overdosing might result fatally, though whether hypercalcemia was the cause of death is obscure. The precise formula and relations of this extract have not been yet determined, but this work evidently marks an important advance. Collip and Clark[1] using the new extract could not save the life of one dog, poisoned with guanidine, but R. H. Major[2] found that in dogs Collip's extract would promptly reduce the persistent arterial hypertension following non-toxic doses of methylguanidine.

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[1] Loc. cit., p. 128.

[2] Medicine, 1924, vol. **3.**

[3] Edinburg Med. Jour., N. S., 1924, **31,** 541.

[4] Jour. Biol. Chem., August, 1924.

[5] Jour. Am. Med. Assn., Soc. Proc., January 31, 1925; Jour. Biol. Chem., March, 1925, p. 393.

It will thus appear that parathyroid physiology is still somewhat controversial.

DISEASES OF THE PARATHYROID GLANDS.

INFLAMMATORY PROCESSES.

Inflammatory processes *per se* are mostly of academic interest. Syphilis and tuberculosis have been reported (Pepere[3]). They probably occur only as accidental localizations of a general infection. Septic invasion of the parathyroids follows from septic processes starting in other parts of the neck.

DEGENERATIVE AND SCLEROTIC PROCESSES.

Of degenerative and sclerotic processes amyloid has been seen. Fatty infiltration of extreme degree is often found at autopsy in subjects clinically free of any suspicion of parathyroid disease. Moderate grades of sclerosis and atrophy are not infrequently noted, but there is such a wide variation in the microscopical appearances of normal glands that the dozens of supposed pathological changes reported by students of all degrees of experience are of only relative significance. It seems probable that chemical ("functional") derangement of the parathyroid secretion, like that of the islands of Langerhans in the pancreas, is not often of a character to be revealed by the crude methods of the microscope.

TUMORS OF THE PARATHYROIDS.

Small cysts are sometimes seen. In the bullock they occur in about 1 per cent of the ordinary glands as they come from the abattoir. In man cysts may or may not "strangle" the blood supply and damage the gland. Microscopical pockets containing

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[1] Jour. Biol. Chem., June, 1925.

[2] Jour. Kansas Med. Soc., June, 1925, references.

[3] Loc. cit., p. 119.

"colloid" are normal at all ages. H. Bergstrand,[1] writing in 1919, stated after a wide review of the literature, that no large cellular tumors of the parathyroids had been exactly identified.

The *parastruma* of Langhans (thus called in analogy to ordinary thyroid struma) is a rare condition interesting only to surgeons and pathologists. Tetany was never noted in any of the cases. An account may be found in Guleke's monograph.[2]

Of pathological changes in general it cannot be too often urged on the student that the normal gland has a wide range of variability. One is hardly qualified to make a diagnosis of morbid changes in these glands until he has already studied the sectioned organs from fifty autopsies on negative subjects.

SECRETORY DISEASES.

The difficulties and obscurities that have attended the slow advance of our knowledge of these glands in the last thirty years have as usual offered a tempting field for unscientific conjecture. The "office-desk scientist" has been seated in glory, and the occasional slip-shod reviewer of literature (especially of the many unconfirmed announcements from unknown observers) has spread far and wide a curious medley of contradictory "facts." A mixed multitude of convulsive and metabolic disorders have been "successfully treated" by an equally mixed assortment of untested and unstandardized commercial and "home-made" preparations of gland. The diseases range all the way from scleroderma and pityriasis rubra to paroxysmal tachycardia, sciatica and enlarged prostate. In many of these startling reports it is not mentioned what other remedies were used, how much the *vis medicatrix naturæ* or the patient's fancy had to do with the "cure," or what the personal equation of the observer was. Parathyroid secretion may, like epinephrine and pituitary extract, presently prove to have a variety of pharmacological uses at the bed-side. But so far much of the evidence offered is far from satisfactory.

Classes of Secretory Disorders.—The parathyroids, like other glands of internal secretion, may theoretically be too active (*hyperparathyroidism*), or not active enough (*hypoparathyroidism*), or entirely inactive (*aparathyroidism*). As to possible perversions of secretion nothing is known; hyperparathyroidism may also be dismissed at once, for no disease has been identified as due to excessive parathyroid secretion. *Postoperative tetany* is the only disease clinically associated with absence of the glands. Clinical forms of hypoparathyroidism are not securely settled, but it is thought probable that most forms of *idiopathic tetany* (including "spasmophilia") are due to acute or subacute parathyroid insufficiency. There are also some grounds for supposing that *paralysis agitans* in many instances (see discussion later) originates as a chronic parathyroid deficiency.

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[1] Loc. cit., p. 118.

[2] Loc. cit., p. 135.

POSTOPERATIVE TETANY.

This is an alarming and dangerous condition developing after operations on the thyroid gland in the course of which the parathyroids have been removed or their blood supply damaged; or after which they have been strangled by scar tissue, or destroyed by infection. During recent years the condition has received a vast deal of attention from surgeons (Kocher, Halsted and a host of others). A recent bibliography is given by M. and K. Grasmann.[1]

Frequency.—In America it is probably a rare occurrence, though surgeons are naturally apt to deny to such unfortunate accidents the publicity they give their successes, and statistics are hard to find. At the Lakeside Hospital, in Cleveland, Crile and Lower[2] state that parathyroid symptoms occur after thyroidectomy, but they give no figures. The existence of accessory glands in unexpected places has probably saved the reputation of many careless or ill-informed operators. Even a single gland with a good blood supply will save the patient's life. In old museum specimens of thyroid tumors removed in the nineties of the last century I have more than once found parathyroids hanging to the surface of the tumor mass. The accident still occasionally occurs. M. and K. Grasmann[3] affirm that on the Continent postoperative tetany is increasing. They attribute it to faulty technique, and they urge especially that all four thyroid arteries should never be tied. Statistics of the occurrence of tetany after goitre operations are studied in elaborate detail by V. Ghiron.[4]

Symptoms.—Symptoms when early and acute resemble the parathyroid tetany of animals, though not all the signs will be present in a single patient. Dreadful restlessness, mental distress, insomnia and delirium are superadded. Signs of idiopathic tetany may sometimes be observed or elicited (p. 136). Occasionally early and severe symptoms gradually subside. Presumably this is due to slow compensatory enlargement of a gland fragment left behind or of a supernumerary gland never disturbed.

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[1] Arch. f. klin. Chir., 1922–1923, **122**, 699.

[2] Crile and Associates: The Thyroid Gland, Philadelphia, Saunders, 1922.

[3] Loc. cit.

[4] Loc. cit., p. 125.

A remarkable *late case* is reported by A. F. Hurst.[1] The patient was a clerk, and when first seen was forty-seven years old. At thirty years he had first noticed a gradually growing thyroid struma. This was later excised. For two years after the operation he was well, and weighed 191 pounds. He then rather suddenly became depressed, nervous, tremulous, restless and could not sleep. There was fibrillary twitching of the eye-lids, but no tetany. His pulse was 120. Although he had a fine appetite, his weight fell gradually away to 141 pounds and less. There were three or four stools a day. He became impotent. His hair stopped growing, and became thinner. He was tormented by dysphagia and colic. On parathyroid medication his recovery was almost miraculous. Relapses occurred once or twice upon omission of the medicine, but at last accounts he was well and had discontinued the parathyroid. Presumably slowly contracting scar tissue strangled his normal parathyroids, and the medicine helped him on until accessory tissue had time to grow.

Diagnosis.—This ought not to offer many difficulties to anyone acquainted beforehand with the symptoms of parathyroid tetany. The most suspicious circumstance at all times, early and late, is the fact of a previous operation for thyroid extirpation.

Course and Prognosis.—Many cases go on to a fatal termination. Death is sometimes sudden. N. Guleke[2] collected 160 cases of postoperative tetany. Of these 25 per cent died, and 17 per cent more were incapacitated. The probable reason for the slow occasional recovery of some of the patients has been already noted.

Treatment.—*Prevention* is all important. I have already noted Grasmann's[3] suggestion that no surgeon should ever tie all four thyroid arteries. The surgical text-books nowadays all give excellent drawings of the anatomical relations of the parathyroids. Modern technique aims to spare them and their blood supply as fully as possible. Should the accident be observed during operation, the damaged or excised gland should be transplanted—not in the operation wound, however, but in some other well-vascularized part of the body. Such grafts (isotransplants) are the only ones giving reasonable chance of permanent growth. To be perfectly sure of the facts a bit of the supposed parathyroid should be reserved for microscopical examination.

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[1] New York Med. Jour., 1922, **115**, 403.

[2] Chirurgie der Nebenschilddrüsen, in Neue deutsche Chirurgie, Stuttgart, F. Enke, 1913.

[3] Loc. cit., p. 134.

When postoperative symptoms first give the grievous news that the accident has occurred, a physiologically tested parathyroid extract should at once be given, both by the mouth and subcutaneously. This medication should be continued from time to time in the hope of tiding the sufferer over the critical period needed for hypertrophy of some surviving fragment of normal gland, or some accessory islet, possibly capable in time of supplying the lack.

Grafting a gland from a suitable human donor may be considered (homoiotransplantation). A few such successful attempts have been reported—so few that doubt may well be cast on all. Gland-grafting is more fully considered in Chapter XIV. The human donor runs a chance, himself, of irreparable harm; and except as an occasional fortunate accident, the difficulties of identifying a gland at the bottom of a deep, bloody and pulsating hole in the neck are practically insuperable.

Human glands removed at autopsy have also been used. A. E. Brown[1] reports a typical experience. Three autopsy glands were planted in the patient's sternocleidomastoid. She was greatly improved for some months, then rather suddenly relapsed and died. Microscopical examination of the grafts showed extensive fibrosis, and the author judged "they were probably not functioning." The older literature is reviewed rather pessimistically by N. Guleke.[2]

An attempt should be made, of course, to relieve the patient's symptoms by the usual sedative drugs and by hypnotics. Calcium lactate may be given intravenously from time to time. The technique, which must be exact, is described in the section on idiopathic tetany. By Freudenberg and György[3] ammonium chloride has been successfully used. Inasmuch as death is sometimes sudden, the patient's friends should be advised of the gravity of his condition.

IDIOPATHIC TETANY.

This disease is also called *epidemic tetany* and *endemic tetany*. Some writers use the word "spasmophilia" in designating some of its minor manifestations.

Etiology.—That tetany is due in all cases to parathyroid deficiency is not an assured scientific fact. S. Vincent[4] doubts it. H. W. C. Vines[5] remarks very correctly, I think: "Tetany is associated with a variety of acute and chronic toxemias. It is an open question how far there is justification for associating all types of tetany with parathyroid failure, and until experimental and clinical evidence is more concise the question cannot be answered."

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[1] Ann. Surg., 1922, vol. **75**.

[2] Loc. cit.

[3] Loc. cit., p. **137**.

[4] Loc. cit.

[5] Loc. cit.

The newer literature continues to contain interesting but inconclusive theories of the origin of tetany. L. F. Barker's review[1] gives some useful references. Collip[2] and Collip and Backus[3] describe tetany as experimentally produced by prolonged violent breathing (hyperpnea) for a quarter or a half hour in healthy young men. The writers ascribe the phenomenon to the abnormal withdrawal of carbon dioxide from the system with resulting alkalosis of the blood plasma. Grant[4] thinks tetany may be attributable to disturbance of the acid-base equilibrium of the blood. Freudenberg and György[5] found ammonium chloride in doses of 3 to 7 grammes a day efficient in relieving 10 cases of infantile tetany and 1 of postoperative tetany. They attribute this to the conversion of the ammonium chloride into urea and hydrochloric acid in the blood, and the consequent creation of an acidosis (an observation of Haldane), which corrects the alkalosis of tetany. All these propositions require confirmation. References and discussion in a recent paper by I. Greenwald[6] are helpful.

So far as I am informed P. Jeandelise[7] first suggested the parathyroid connection. F. Pineles,[8] J. Erdheim[9] and W. G. MacCallum[10] followed up the subject, none of them successfully explaining all the facts. The difficulties of interpreting *post mortem* appearances in the parathyroids have been already noted. The comparative rarity in parathyroid tetany of the mechanical excitability of the motor nerves so marked in idiopathic tetany, and the frequent absence of tremor in idiopathic tetany, are also points of difference. But the parathyroid hypothesis has been generally accepted, and may be provisionally allowed.

Predisposing Causes.—Predisposing causes are gastric dilatation, pregnancy, and in children such common conditions as rachitis, worms and chronic indigestion. Von Hochwart,[11] whose excellent monograph has been a classic source of information for all subsequent writers, connects certain cases with the acute infectious diseases and with various chronic intoxications.

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[1] Jour. Southern Med. Assn., 1923, **16**, 571.

[2] Canadian Med. Assn. Jour., 1920, **10**, 935.

[3] Am. Jour. Physiol., 1920, **51**, 568.

[4] Arch. Int. Med., 1922, **30**, 355.

[5] Klin. Wchnschr., 1922, **1**, 410.

[6] Jour. Biol. Chem., October, 1922.

[7] Thèse de Nancy, 1903.

[8] Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1904-1905, **14**, 120.

[9] Ibid., 1906, vol. **16**.

[10] Centralbl. f. allg. Path. u. path. Anat., May, 1905.

[11] Die Tetanie, 2d ed., Wien and Leipzig, 1907.

Distribution.—Adult tetany in America is rare. The occasional cases occurring in New York in hospital wards are exhibited to classes and visiting physicians as extraordinary and notable phenomena. Among the scattered notices in American literature hardly 100 cases can be found. In children it is more common. On the Continent it is common at all ages. In Vienna in former years Friedrich Kraus used to show his classes a long succession of cases. He remarked that it was specially common among shoemakers' apprentices. McCarrison[1] states that in the Himalayas in the spring it is endemic, especially among child-bearing women.

Symptoms.—The essential element in the disease is increased excitability of all the nerves, autonomic and voluntary, sensory and motor. The motor excitability is manifested not usually by tremor or stiffness, but by spasms. Spasms are tonic, with intermissions. They may be local, general, unilateral ("hemitetany") or bilateral. A sharp tap on the trunk of the facial nerve before the ear may produce a variably strong contortion of the facial muscles of the same side. This is called *Chvostek's sign*. Its value has been recently much called in question. Compression of the trunk of the brachial nerve in the arm (Hochwart advises that it must sometimes be kept up for three to five minutes) produces a coördinated spasm of the muscles of the forearm, *main d'accoucheur*, "obstetric hand;" the fingers are extended and clumped, the thumb in the palm. Trousseau first described this sign, and it is still called by his name (*Trousseau's sign*). In severe cases a blow on a nerve trunk produces a general tonic convulsion which may last for hours. The patient remains conscious, and suffers great pain. There is not usually any continuous tremor, though it is mentioned as an occasional occurrence.

In children there may be nothing but carpopedal spasms (*arthrogryposis*), but when these persist for any length of time they become very painful, and the patient screams continuously. Laryngismus and glottic spasm also occur in babies, and general convulsions are not unknown. The convulsions are sometimes fatal, but not often. Infantile symptoms are generally benign, yielding to treatment in a few weeks.

Diagnosis.—The diagnosis will depend on a rational interpretation of the signs. In babies carpopedal spasms may appear in a rather wide variety of conditions having no relation to tetany or to one another. A little care will distinguish them. True tetanus is a dangerous disease of entirely different causation, and is apt to be marked first cf all by trismus, which fortunately is rare in tetany. Hysterical contractures are puzzling at times, but the age and sex of the patient, and the coëxistence of signs of hysteria elsewhere have usually solved the question without much difficulty.

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[1] Die Tetanie, 2d. ed., Wien and Leipzig, 1907.

Treatment.—The predisposing causes must be looked for, and when possible removed. Conceivably abortion may be necessary in severe cases complicating pregnancy, but in America the attacks are not usually grave enough to require so drastic a remedy. Tetany with gastric dilatation may require operation. In children, rickets, worms and intestinal toxemias must be cared for in the way proper for each trouble.

To adults severely ill parathyroid may be given. There is ample evidence nowadays from many sources that it is an efficient remedy. When the stomach is dilated, or the bowels disturbed, hypodermic injection of the same remedy should be made. (See section on Parathyroid Therapeutics.) In very severe cases temporary relief may be got by intravenous injection of soluble calcium salts. Calcium lactate is usually given. The dose is 1 or 2 gm., though Moffitt[1] recommends much larger amounts. The vein at the elbow is, as usually, distended by a compress. An aqueous solution of calcium lactate, of measured strength, is filtered clear, boiled for ten minutes in a sterile, cotton-plugged test-tube placed upright in a water-bath, then cooled to 105° F., and slowly injected *secundum artem*. The technique must be correct; calcium salts in the tissues make a painful induration, sometimes an abscess. Sealed tubes of injectable calcium salts are now obtainable in the shops when it is more convenient to use them than to make one's own. Calcium salts *per os* are imperfectly absorbed, and in urgent cases one should not lose time by trying out such a doubtful source of help. Besides these remedies warm baths may be employed, and proper doses of bromides, or $\frac{1}{4}$ to $\frac{1}{8}$ gr. of luminal. Warm cleansing enemata are helpful. In dilatation of the stomach lavage is apparently indicated; but sometimes it seems to do harm instead of good. Ammonium chloride in doses of 3 to 7 gm. has been recommended (p. 137).

The patient should be put to bed and carefully fed on a diet suited to the individual case. Inasmuch as tetany is quite as severe in cabbage-fed rabbits as in meat-fed dogs, one cannot *a priori* be quite sure that meats should be entirely excluded from the diet. A little careful experimentation may be needful.

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[1] Jour. Am. Med. Assn., 1911, **57**, 452.

To infants also parathyroid may be given. Calcium by the mouth was recommended long ago by European writers. In this country, however, the simpler household remedies are more popular. The bowels must be regulated, worms and worm eggs looked for in the stools, rickets treated with fresh air, sunshine and the fat-soluble vitamins of cod-liver oil. Laryngismus is to be treated as elsewhere, with warm baths, inhalations of hot water vapor from a croup kettle, and small doses of wine of ipecac and bromides. Convulsions may require chloroform. Fortunately they are not often so quickly fatal as to forestall treatment.

ECLAMPSIA NEONATORUM.

Convulsions in the new-born, or in very young infants, have also been attributed to parathyroid dysfunction. There is fair reason for supposing that in prolonged vertex presentations, the tissues of the infant's neck are unduly compressed, with injury of the parathyroid blood supply as a result; but the proofs are inadequate. The difficulties incident upon the identification of infants' parathyroids at autopsy have been already noticed. The pathological appearances reported in the glands found are far from convincing. The alleged cures have been produced with parathyroid often of doubtful quality, and in infants in whom, of course, the diagnosis was only clinical.

Infantile convulsions are very generally a difficult problem. Apart from *intrapartum* damage to the central nervous system, early infantile convulsions occur from hyperpyrexia, from worms, from phimosis, from indigestion, from rickets, from atelectasis, from pertussis; and there are "idiopathic convulsions" without any known cause at all. Before parathyroid was discovered these patients got well from time to time on a variety of treatments. If they now recover on parathyroid therapy one only asks that the above facts be considered before the relation between disease and remedy is declared to be more than accidental.

Parathyroid at least does no harm. It should be given hypodermically. Intravenous calcium injections are also a rational resort. The technique has been already described.

PARALYSIS AGITANS.

Synonyms.—*Parkinson's disease;* "shaking palsy."

James Parkinson's classic account of paralysis agitans appeared in London in 1820. In the grandiose Johnsonian prose of the period he remarks in his Preface: "The disease respecting which the present inquiry is made is of a nature highly afflictive. . . . The writer will repine at no censure which the precipitate publication of mere conjectural suggestions may incur, but shall think himself fully rewarded by having attracted the attention of those who may point out the most appropriate means of relieving a tedious and most distressing malady."

I shall not dwell upon the literary history of shaking palsy. The story would take a long time and fill many books. The symptomatology of Parkinson's original account is quite full. Later writers have added *paralysis agitans sine agitatione* and a rarer form *with shaking* but *without* any marked *rigidity.*

Etiology.—All races of men appear susceptible. Charles W. Burr[1] has reported a case in a negro of advanced years, and expresses the opinion that the supposed immunity of the negro race to this disease is an error.

As regards age incidence, it was believed for a long time that paralysis agitans is strictly confined to the second half of life, not appearing before the third decade. H. Willige[2] has, however, carefully reviewed the literature, and thinks that some of the reported cases occurring as early as the twentieth year must be acknowledged as genuine. Several of these he considers "familial," and evidently a "special type." J. R. Hunt[3] has reported a case of the paralysis agitans syndrome beginning in the fifteenth year of life. The autopsy showed what Dr. Hunt designates as "destructive lesions of certain groups of cells in the globus pallidus." He, too, believes the young patients constitute a special type, and thinks that further study will differentiate also many of the older cases. His views have received partial confirmation from later French writers. The literature contains many other pathological hypotheses based upon one or two autopsies and without subsequent confirmation. Every now and then some tyro announces that the lesion is luetic; but 90 per cent of the Wassermanns are negative.

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[1] Jour. Am. Med. Assn., January 4, 1913.

[2] Ztschr. f. d. ges. Neurol. u. Psychiat., 1911, **4**, 4.

[3] Proc. Am. Neurol. Soc., Washington, 1916.

The confusion and contradictoriness of autopsy reports long ago led C. L. Dana and others to advance the view that a chronic toxemia lies at the base of the disease. It was suggested by Lundborg,[1] of Stockholm, and by myself[2] independently, that a *chronic dyscrasia or insufficiency of the parathyroid glands* is quite possibly the cause of the disease. Victor Horsley[3] had already hinted at the possibility, but he supposed the thyroid to be at fault.

Reasons for this view may be summarized as follows:

1. The symptoms appearing in rabbits and other convenient experimental animals upon removal of the parathyroid glands are suggestive; shivering and twitching of the voluntary muscles, rigidity, convulsions, salivation, and often a quite typical "propulsion" may be observed. Vetlesen[4] discusses this question at length, and concludes: "It is experimentally proved, especially by Tanberg, that by operation on animals a special chronic form of parathyroid insufficiency may be produced which clinically presents a striking similarity to paralysis agitans in man."

2. The disease has been reported several times in conjunction with myxedema and with exophthalmic goitre, where the contiguity of the diseased thyroid might well be supposed to work mischief to the parathyroid.

3. The parathyroid glands have been reported in a diseased condition in a fair percentage of the autopsies upon cases of paralysis agitans. Not much importance, however, attaches to this. *Postmortem* deficiencies are deceptive. Some writers report normal glands; some even report hyperplasias. Anyone who will take the trouble to consult A. Biedl[5] or B. Breitner[6] will realize for himself how little truth is to be found in the babel of contradictory voices.

4. Finally, the use of a properly prepared parathyroid extract by the mouth, or better, by hypodermic administration, has been productive of remarkable benefit in a majority of the cases treated. This therapeutic test has been applied to hundreds of cases during a period of more than ten years past; the treatment has shown a steady and gratifying increase in popularity. The effect *may be* pharmacological, but it is worthy of note.

Admittedly these considerations are by no means a demonstration of the etiological relation of certain forms of shaking palsy to parathyroid insufficiency; but the hypothesis comes within the bounds of reasonable scientific speculation.

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[1] Deutsch. Ztschr. f. Nervenh., 1904, **27**, 217.
[2] Med. News, 1905, **87**, 1060.
[3] Brit. Med. Jour., 1885, **1**, p. 111.
[4] Ztschr. f. d. ges. Neurol. u. Psychiat., 1914, **26**, 462.
[5] Loc. cit., p. 17.
[6] Deutsch. Ztschr. f. Chir., 1923, **182**, 380.

By the profession both here and in Europe during the last twenty years the parathyroid theory has been received with considerable favor. In *International Clinics* for 1912 I reviewed the literature, mostly favorable, up to that date. Since then I. Greenwald[1] has advanced some interesting, but I do not think conclusive, chemical considerations against the parathyroid theory. Troemner[2] thinks the glandular hypothesis "possible;" Schioetz[3] defends it with some enthusiasm.

The present view of the etiology of the disease must be conservative. The "agitans syndrome" may result from the operation of more than one cause. The observations of Hunt and Willige just quoted point in this direction, and it must assuredly be admitted that the cases of "agitans syndrome" (called by German writers "Parkinsonismus") appearing since 1918 after an acute or subacute attack of epidemic encephalitis, or severe influenza, are of a peculiar character quite unlike the familiar clinical form of our older experiences.

If the lesion described by Hunt in the globus pallidus receives further confirmation one must still explain its appearance. In itself it is a part only of the pathological anatomy of the disease. No blocked artery has ever been found. Some chemical or bacterial poison with a selective affinity for this region of the brain must be presupposed.

The precise mode of production of excessive muscular tonus in paralysis agitans is also doubtful. F. M. R. Walshe[4] found the rigidity of paralysis agitans much relieved by intramuscular ("motor point") injection of 10 to 25 cc. of 1 per cent sterile novocaine. The injection, in his view, served to "de-afferent" the muscle. Tremor, however, was unaffected.

From the studies of Hunter and Royle,[5] it appears that the tonus of spastic paralysis in one limb can be magically relieved by cutting the ramus of the sympathetic nerve supplying the part. It is, therefore, tempting to suppose that the tonus of paralysis agitans is also due to irritation of the sympathetic rather than the voluntary motor nerves. Exactly how a lesion at the base of the brain can produce this excessive localized sympathetic irritation has not been worked out. C. D. Camp[1] believed he found a primary irritative lesion of the muscle bundles in paralysis agitans, but this observation also, so far as I am aware, has failed of confirmation.

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[1] Am. Jour. Med. Sci., 1914, **147**, 225.
[2] Deutsch. Ztschr. f. Nervenh., 1914–1915, **53**, 38.
[3] Ztschr. f. d. ges. Neurol. u. Psychiat., 1914, **23**, 88.
[4] Jour. Physiol., 1923–1924, vol. **58**.
[5] Loc. cit., p. 31.

Intravenous injections of calcium lactate I have not found to have any influence on the rigidity of Parkinson's disease. So far as I am acquainted with the literature, the percentage of guanidine in the blood and urine of these patients has not been investigated.

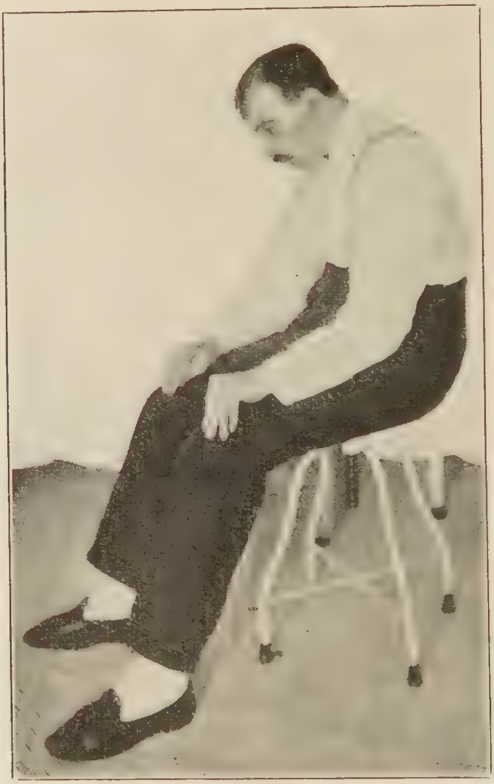

FIG. 28.—Middle-aged man, with Parkinson's disease, showing facies, posture, flexor contractures of forearm muscles.

Symptoms.—If current researches on the relationship of the sympathetic nervous system to muscular tone (see above) are confirmed, the symptoms of paralysis agitans may be largely referred to irritative impulses of the sympathetic system of nerves. The disease is characterized essentially by *increased tone of the voluntary muscles.* When muscle-contracting influences are clonic, tremor is produced. When they are tonic, rigidity follows (Fig. 28). Both signs are usually present; when the former predominates tremor may be the striking feature; when the latter, *paralysis agitans sine agitatione* is observed. The latter is a much graver and more progressive type of the disease. The tremor in 95 per cent of the cases is absent in sleep. It is slow, 3 to 6 vibrations a second; aggravated by excitement and only temporarily controlled by the will. It begins as a rule in one hand or finger or thumb, or in one toe; the fingers often show a pill-rolling or cloth-smoothing movement. In the lapse of weeks and months it spreads to adjacent groups of muscles in the same limb and to other parts of the body. Arm and leg of one side may be simultaneously affected with a simulation of hemiplegia, but the tendon reflexes are not altered. Speech is labored; the face is mask-like (Parkinson's

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[1] Jour. Am. Med. Assn., April 13, 1907.

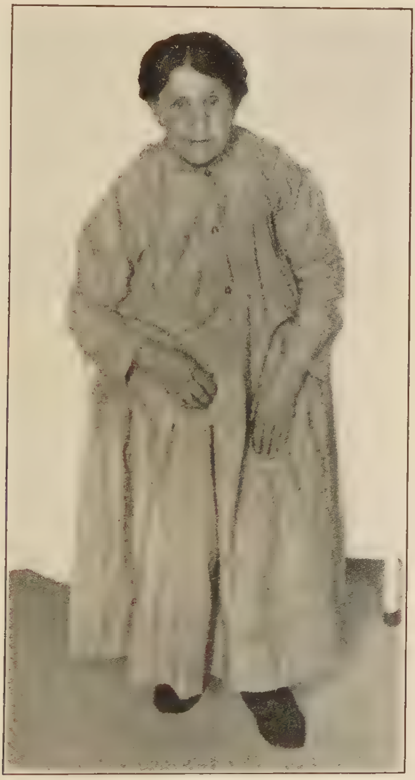

Fig. 29.—Woman, aged fifty-five years, showing "Parkinson's mask," typical posture of body, edema of hands and forearms.

mask, Fig. 29). The tongue sometimes vibrates uncontrollably. Saliva is increased, and may drip from the mouth. "Propulsion" and "retropulsion" are familiar signs that all the text-books describe in full. "Lateropulsion" has also been noted.

Muscular and fascial pains are tormenting. Restlessness is a common symptom; the patient may have to be turned in bed every five minutes. Dropsy of hands and feet, sometimes also of forearms and legs, is common. It seems due merely to the persistent muscular rigidity. Hot and cold "flushes," or a more persistent sense of heat or cold all over the body, indicate that the vasomotor fibers of the sympathetic are also disturbed. Except in the cases following "sleeping sickness," the mind remains clear, though psychasthenic fears may be met with. The despondency that patients manifest is a natural outcome of their own realization of their distressing condition.

Diagnosis.—This is not usually difficult when the student has had one case well explained to him. Hemiplegia has a history of relatively sudden onset, and shows increased reflexes on the paralyzed side. Tremor senilis is unaccompanied by pain, rigidity or any of the other symptoms of paralysis agitans. Toxic tremors are much finer and faster. Early cases of paralysis agitans with tremor of intention (Gowers) are more perplexing, but time will tell.

Prognosis.—The disease when first appearing in the latter half of life may continue indefinitely, and with careful treatment may progress very slowly. Remissions are not uncommon, even in the less favorable forms. The cases with rigidity only are apt to get worse very fast. Heart disease, high blood-pressure, or an enlarged prostate may end the scene long before the symptoms of paralysis agitans have grown unbearable. Cases in young people are rapidly progressive and yield less readily to treatment. The agitans syndrome following epidemic encephalitis is a very difficult condition, for which almost no relief can be found in the way of treatment. Some of these patients are heard of after a year or so in an insane hospital. Some, on the contrary, get better. In respect to these patients, the prognosis should be especially reserved. Parathyroid does them no good for any length of time as far as I have observed.

Treatment.—*Parathyroid Gland.*—The gland preparation used should be tested and standardized (see Parathyroid Therapeutics). One-twentieth to $\frac{1}{50}$ gr. of the acetic extract a few times a day should be given by mouth. By hypodermic injection the dose is $\frac{1}{50}$ gr. Sometimes the patients do better by combining oral and hypodermic treatments, perhaps three tablets a day and one hypodermic at bed-time.

The effects of parathyroid in favorable cases are in every way beneficent. The rigidity and tremors are controlled, salivation diminished and restless and insomnia relieved. Occasionally quite a miracle is worked, as in a case reported by George Martyn.[1] Dr. Martyn's patient got out of bed, began again to dress and feed himself, and reassumed his old job of pruning his orchard trees. His improvement was interrupted only during the time when his supply of medicine ran short. A medical correspondent in Cleveland wrote me of a lady who rose from bed, where she had lain "like a wooden image," dressed and fed herself, and even recovered her singing voice which had been lost for years. She received fresh glands, a dozen daily by mouth. Dr. Martyn's case responded only to hypodermics. A medical friend in New York told me recently that his father, long a sufferer from the disease, had been virtually kept alive by parathyroid for ten years. Of another elderly patient living near New York, his daughter wrote me: "I should dread to contemplate my father's declining years without the help the parathyroid has given him." The wife of another recent patient writes: "We are greatly encouraged; we hope he will yet be entirely well."

Contraindications.—There are none, unless one should speak of the idiosyncrasies for parathyroid, which are mentioned in the next section. Improvement begins usually in a few weeks, and continues for a few months. After this the patient remains in a relatively stationary condition—not "cured" any more perfectly than a cretin is cured by thyroid, but relatively comfortable. With continued medication the favorable cases get on quite well for years, and pass their three-score-and-tenth year with no greater inconvenience than in one way or another generally befalls old age.

Failures of the Parathyroid Treatment.—I have already mentioned that the "agitans syndrome" following encephalitis or influenza ("Parkinsonismus") is not benefited for any length of time by parathyroid. At least such is my own experience.

Among the patients certainly not of this type institutional cases do not do well. The reasons are not far to seek. But after good success with 4 or 5 patients in comfortable private life there usually come 2 or 3 more which are failures—patients in whom even prolonged and excessive dosage with tablets and hypodermics has no effect. About 60 to 70 per cent only of a large number of patients will be benefited. Then there are patients who do excellently for a year or so, but later rapidly relapse. Physicians who have seen only two or three failures are pessimistic. Those who have had two or three brilliant successes are just as unjustifiably optimistic. The truth lies between. The cause of failure may possibly lie in the differences between human and animal parathyroids. S. P. Beebe (p. 112) called attention some years ago to the notable efficiency of human thyroid extracts in hypothyroid conditions as compared with animal extracts; but this is only conjecture.

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[1] The Link, Los Angeles, February, 1917.

If I may judge from year-long personal observation and experiment, there are no other internal secretions, either alone or in combination, which have any specifically beneficial effect in paralysis agitans. Among the older patients pineal gland is probably a useful stimulant for failing mental activity, and there is now on the market one extract of pancreas which seems to be valuable in the peculiarly obstinate constipation these patients are afflicted with. I cannot too strongly deprecate promiscuous dosing with thyroid, pituitary and others of the internal secretions; thyroid especially does serious harm. Even massage of the neck over the thyroid gland sometimes liberates into the circulation enough thyroid secretion to make the patient distinctly uncomfortable. This is, I imagine, why so many of these unfortunates come to me with the story that they have already been "almost killed" by the osteopaths.

Other Remedies.—*Hyoscine*, belonging to the belladonna group of alkaloids, is a symptomatic remedy of some value. H. C. Wood introduced it nearly forty years ago. In a general way, it acts like atropine, drying the throat and dilating the pupil. In paralysis agitans it may be occasionally given in small doses to tide the patient over some emergency—a church service, a dinner, a journey. Hyoscine hydrobromide in doses of $\frac{1}{200}$ gr., by mouth or subcutaneously, is the preferable form of administering the drug. *Duboisine* sometimes works better, but not often. M. Allen Starr preferred *hyoscyamine*. Overdosing is dangerous; delirium, urinary retention with overflow, paralyzed accommodation and the other signs of belladonna poisoning result.

The bromides and antispasmodics may sometimes help for a while. The hypodermic use of arsenic (sodium cacodylate, 1 to 5 gr. daily) is sometimes beneficial. Rhamnus purshiana is the most valuable remedy for the dreadful constipation these patients often have. Calcium does no good in any form. Even large intravenous injections have failed in my hands.

Remedies other than drugs should not be forgotten. Warm baths at bed-time are helpful; sea salt increases the efficiency of the warm water in the opinion of some patients. General massage and passive motion sometimes comfort the sufferer. Massage of the front of the neck, however, is by all means to be avoided, for reasons already stated. Easy travel is helpful; exercise (horseback, motor or walking when practicable) is to be recommended. Patients should be kept out of a hospital environment as long as possible.

The *diet* should be laxative, but there are otherwise no special reasons why a vegetarian diet should be imposed. After many dietetic experiments of all possible kinds, and many special collations of food and salts, I have returned to the recommendation of a simple balanced ration suitable to the age and tastes of the patient and modified only by the requirements of existing complications.

As the worst cases sometimes have remissions, the medical attendant is always justified in maintaining a hopeful attitude in the sick-room.

Grafting into the human patient of animal parathyroid glands has been tried, of course, and of course with "encouraging success." Such reports are to be taken with great reserve (Chapter XIV). W. Kühl[1] quotes some recent literature, and thinks that failures have been due not to heteroplastic tissue being used, but because it was not fresh, not warm, or not sterile, or that it was tried upon "Parkinsonismus" instead of true paralysis agitans. Some of the grafts were chosen haphazard and not microscopically identified.

The wonderful effect of the *sympathectomy* of Hunter and Royle (p. 31) upon the rigidity of spastic paralysis has roused the hope that paralysis agitans might also be amenable to treatment by cutting the sympathetic rami supplying the stiff extremities. Up to the present time, however, the results have not been encouraging. Indeed, I am told by Dr. Allen B. Kanavel (personal communication) that it is virtually proved that the Royle and Hunter operation will not benefit this condition. Dr. N. D. Royle himself kindly writes me (September 18th, 1925) that in his experience "Ramisection improves the trouble to a certain extent, but the tremor persists."

PHARMACOLOGY, THERAPEUTICS AND ADMINISTRATION.

To the extreme confusion that has attended parathyroid therapy in the last twenty years I have already adverted. Almost anything in the way of a medicament has had to do duty. A series of cases was reported some years ago by two German observers who got wonderful clinical results from feeding their patients with a raw hash made of "all the tissues in the neck of the sheep around the thyroid gland." The hope was cherished that among the lymph nodes, accessory thymuses and thyroids, hemolymph nodes and fat an occasional parathyroid might be included; they had not been able to identify the sheep's gland more exactly.

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[1] Deutsch. Ztschr. f. Chir., 1924, **187**, 328.

Much of the parathyroid now on the market appears to have been made from similar material. It is often entirely inert. Use of such material has led to grievous misapprehensions, both positive and negative.

Material.—In America bullocks' glands are the best available raw material. Theoretically the glands ought not to be taken from castrates—only from cows and bulls. But this objection does not seem practically to hold good, if one may judge from the prompt effects of bullocks' glands on laboratory tetany and on the symptoms of properly selected patients. In countries where properly inspected horse meat is used for food, horse glands are, I am told, sometimes employed.

Raw bullock glands have been successfully used for therapeutic purposes, but one need not stop to say how impracticable this is as a general resort. The glands go bad, they fail of digestion, they cannot be properly assayed, they are only available in the close neighborhood of abattoirs, and when the stomach rejects them they cannot be given by hypodermic.

Raw beef gland is very fatty. Market preparations of whole gland have usually been defatted by some solvent like acetone; acetone will remove the fat, but it seems also to damage or remove much of the active principle of the cells.

Berkeley and Beebe[1] described a process for nucleoproteid extraction from bullock glands. They found that this nucleoproteid (which is really an *acetic precipitate*), dissolved in saline, and injected in one small dose into a dog with tetany, will relieve the symptoms in fifteen minutes and abolish them in about two hours. Relief persists for twelve to twenty-four hours. Digestion mars and boiling destroys the activity of this preparation. We found that the albumins and globulins of the same glands had no effect. This does not by any means prove that the active principle of the parathyroid belongs to the nucleoproteids; the colloid particles may carry down a number of other substances by adsorption. Collip's preparation (p. 131) bids fair to be still more active. Its introduction into practice may clear up much of the obscurity that now attends parathyroid medication.

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[1] Loc. cit., p. 127.

Standardization.—The physiological try-out on a dog serves very well to standardize in a general way the activity of any parathyroid preparation. By weighing the dog and weighing the amount of extract, and noting the degree and duration of relief, a roughly correct conclusion may be reached.

Vines[1] has stated that the activity of a commercial preparation of parathyroid, in respect of the effect on calcium content of the blood, may be roughly estimated by incubating the unknown material in acid solution with a measured amount of guanidine. He is doubtless correct in saying that parathyroid nucleoproteid will not act in this way upon guanidine, for no nucleoproteid is soluble in an acid medium.

Dosage.—The parathyroid preparation that I have described is for sale by several New York dealers, both as tablet and hypodermic. The hypodermic is made isotonic with blood serum by adding salt in proper amount. If aseptically injected it should not cause the slightest local reaction. The dose is $\frac{1}{50}$ gr., one or more times a day. Commercial dried gland used by Vines and Grove was effective, they thought, in doses of $\frac{1}{10}$ gr. per day. Collip's preparation in large doses is said to cause a dangerous degree of hypercalcemia in experimental dogs, but in the ordinary course of clinical work with the preparations at present available no harm ever results. I had one patient who thought that the remedy constipated him, but this complaint was readily relieved by a gentle laxative. Some paralysis agitans patients complain of increased "nervousness" when starting out with too large a dose. This is to be corrected by stopping the remedy for two days and then beginning again more cautiously.

Idiosyncrasy for Parathyroid.—Out of the hundreds of patients with Parkinson's disease whom I have seen or personally cared for, only one, a Canadian gentleman, aged sixty-two years, could not take beef parathyroid. The smallest dose poisoned him apparently and made his symptoms much worse. Dr. C. G. Parcher, of Saugus, Mass., wrote me in 1917 of a lady with paralysis agitans in his care who seemed to have a nervous crisis ("a terrible drawing feeling through the body") whenever she took more than one dose. The condition recurred on later trials of the medicine. Dr. Parcher seemed in doubt as to the hysterical element in the case. Morris[2] had a patient who took large doses of parathyroid for a while, and finally developed a psychosis. The psychosis improved when the parathyroid was stopped. M. Critchley[1] noticed diarrhea in children. It stopped when the dose was discontinued and began again when the parathyroid was resumed. Considering the large number of patients who have been treated with the remedy, the above does not seem to be an alarming record.

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[1] Loc. cit., p. 128 (foot-note).

[2] Jour. Lab. and Clin. Med., 1915, **1**, 26.

Parathyroid Gland in Convulsive Diseases.—On general principles it might easily be inferred that parathyroid gland will be symptomatically useful in many convulsive diseases. As a matter of fact, its use has been suggested and reported successful in epilepsy, in puerperal eclampsia, in chorea, in "spasmophilia," and even in Graves's disease.

As regards *epilepsy* too little is known of its etiology and of its relations to the parathyroid secretion to justify any serious conclusion. The most enthusiastic advocate of parathyroid therapy in epilepsy goes no further than to say that the fits are "less frequent" during treatment. The fits are often "less frequent" for months at a time without any special treatment or any other known reason, and the difficulty of carrying controls along with the treated cases is practically insuperable. The suggestion dates back to the early speculations of MacCallum and Vassali. It has been recently resuscitated by Bisgaard and Hendricksen[2] and by A. Bisgaard.[3] They base their conclusions on the rather slender ground that the "dysregulation" of the hydrogen-ion concentration of the blood in postoperative tetany is also to be observed in epilepsy.

I know of no one in New York to-day who any longer puts faith in this line of treatment—at all events with the preparations of parathyroid now clinically available. The same observation may be made of *eclampsia gravidarum*, which is an entirely different disease from the tetany of pregnant women.

The use of parathyroid in *Graves's disease* is thought to be justified by the supposed "antagonism" between the two glands. This "antagonism" will be mentioned again (Chapter XIII). Various authors have contributed the conventional list of "cures" and "improvements." It is not impossible that parathyroid in proper doses may have a symptomatic benefit on the cases where tremor is very marked, but the results have been very indecisive in my hands.

[1] Quoted by Vines (Loc. cit., p. 128, foot-note).

[2] Zeitschr. f. d. gesam. Neurol. u. Psych., 1922, vol. **78**.

[3] Acta Med. Scan., 1924–1925, vol. **61**.

As to "spasmophilia," not much of this supposed disease is left when all the evident tetanies are taken away and classified where they belong. As to *chorea,* reports of benefit from parathyroid are usually obscured by failure to state whether the patient received, besides, the standard treatment with arsenic. A symptomatic effect of a general antispasmodic character might be reasonably expected.

A short study of the relations of the parathyroids to *eclampsia neonatorum* will be found on page 140.

Parathyroid in Non-convulsive Diseases.—Vines has made an interesting argument for the treatment of chronic suppurative states with parathyroid on the ground that in many such cases (varicose ulcer, bed-sore, gastric ulcer, pyorrhea) the calcium of the blood is reduced, and in raising the calcium percentage of the blood parathyroid fortifies the bacterial defences of the body (p. 131).

H. H. Scott[1] found the ionic calcium of the blood diminished in the dangerous and obstinate disease *tropical sprue.* Giving calcium caused improvement; giving calcium and *parathyroid* caused more rapid improvement and apparent cure. In Manson's *Tropical Diseases* (7th ed.) is to be found the curious note in this connection that an "irregular practitioner" in Shanghai in former years got up quite a reputation for the treatment of this disease with a secret remedy. The drug was supposed to be some form of lime, probably powdered cuttle-fish bone.

Just how the odd mixture of other "cures," such as that of enlarged prostate, paroxysmal tachycardia,[2] arthritis deformans, psoriasis,[3] and peripheral neuritis, are to be explained is more than the author of this volume undertakes to say. They are too few, as yet, to have been removed from the class of accidents.

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[1] Ann. Trop. Med. and Parasit., 1925, **19**, 23.

[2] Dukes: Brit. Med. Jour., 1921, ii, 987. Corney: Lancet, 1922, ii, 863.

[3] Wilson, C.: Brit. Med. Jour., 1924, i, 772.

CHAPTER VI.

PITUITARY GLAND (HYPOPHYSIS CEREBRI).

Name.—The Greek name *hypophysis* refers merely to the situation of the gland under the brain. The Latin name *pituitary* is from *pituita,* meaning spit, mucus or phlegm. The old anatomists supposed that the pituitary gland secreted mucus into the nasopharynx.

Before its glandular nature was known, the pituitary, like the thyroid, was called in a more non-committal way a "body" instead of a gland.

ANATOMY OF THE PITUITARY GLAND.

Gross Anatomy.—The pituitary gland lies in the *pituitary fossa,* or *sella Turcica,* which is located about the middle of the base of the skull and above the body of the sphenoid bone. The pituitary fossa, or "sella," as it is usually called, is of variable dimensions. In profile roentgen-ray photographs the measurements for the (presumably) normal male adult skull run as high as 14 by 15 mm., with proper reductions for women and children. Of the three *clinoid processes* ("bedposts," κλίνη, bed) on each side, the *anterior* are usually flat and horizontal, running backward so as partially to cover in the fossa. The *posterior* processes are more vertical. The *middle* processes are not so high nor so prominent; they often fail to show at all in a roentgen-ray profile. The posterior processes rise from the posterior bony wall of the sella; this wall is called the *dorsum ephippii.*

The sides of the sella are bordered by the grooves for the cavernous sinuses, and above and in front, between the anterior clinoids, is the *optic groove,* which supports the *optic commissure* and terminates on either side in the *optic foramen.* Any enlargement of the pituitary body is therefore apt presently to compress the commissure more or less and cause choked disk and failure of vision. The base of the sella is a thin plate of bone which forms the roof of the sphenoidal sinuses or cells; these open in front into the nasopharynx.

To the clinoid processes the dura mater, *tentorium sellæ*, is firmly attached, roofing in the sella and separating it from the brain. Through the center of this dural covering there runs upward to the *tuber cinereum* a small prolongation of the pituitary gland called the *infundibulum* or *pituitary stalk*. Even in a large bullock this stalk may not be more than 2 or 3 mm. in diameter. In some animals it is hollow above and contains a diverticulum of the third ventricle. In the cat it is hollow all the way to the center of the posterior lobe of the gland (Herring[1]).

Lying in the sella Turcica is the *pituitary body*. The entire gland is an elongated ellipsoid about the size of a large kidney bean. The average dimensions in man are 6 by 8 by 14 mm., the long diameter being the horizontal lateral one. It divides itself naturally into two parts, *anterior lobe* and *posterior lobe*, which are partly separated by a slit or cleft, the remains of the epithelial cup of oropharyngeal ectoderm (Rathke's pouch) from which the gland is developed in the embryo (see Development, p. 159). The anterior lobe is the larger. In the bullock it is about seven times as large as the posterior, and the posterior gland is somewhat like a small inverted cone, occupying the upper posterior part of the sellar space, and continuous there with the tissue of the stalk, which has just been described as connecting with the tuber cinereum. The posterior lobe in the bullock is readily separated from the anterior; indeed, it partly falls away of itself as soon as the capsule of fibrous tissue and dura is trimmed away. It should be carefully noted that this cleft is a *blind sac;* it does not connect either with the subdural space or with the infundibular diverticulum of the third ventricle (For one possible exception, see Herring[2]).

As to *weight*, the work of A. Schoenemann,[3] though done a good while ago, seems to have been later confirmed. Schoenemann's studies indicate that the gland grows with the body, attaining a maximum weight between thirty and fifty years, and thereafter growing a little lighter:

	Averages.		Averages.
New-born	0.13 gm.	30 years	0.80 gm.
10 years	0.33 "	50 "	0.60 "
20 "	0.54 "		

The range of weight in individuals, however, is quite wide.

Histology.—The *anterior gland* (*pars anterior propria*) is yellowish and soft on section (Fig. 30). It contains only a small amount of connective tissue, and is made up almost entirely of cells, with small vessels. Some cells, microscopically, are found to stain badly (chromophobe); these are the most numerous, and are called *chief cells*. Other cells stain well with eosin (*eosinophile*) or with basic dyes (*basophile*). No specialized relation of these various types of cells to the secretory activity of the gland has been discovered. The chief cells are said to be larger and more numerous in the hyperplastic glands of pregnancy.

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[1] Loc cit., p. 160.

[2] Loc. cit.

[3] Vichow's Arch. f. path. Anat., 1892, **129**, 310.

The *posterior gland* is made up of two parts, *pars intermedia* in front and *pars nervosa* behind (Herring[1]). The *pars intermedia* is a thin layer of presumably secreting epithelial cells to be found on the anterior edge of sagittal sections. This layer covers the posterior surface of the cleft, where it lies directly against the anterior lobe, and is actually continuous above and below the cleft with the anterior lobe cells. It is of variable thickness. Chains of cells and individual cells penetrate the supporting framework of the pars nervosa behind, and run up the stalk, tending in the monkey (Herring) to spread (Fig. 34) over the under surface of the hypothalamus, and even penetrate the substance of the brain.

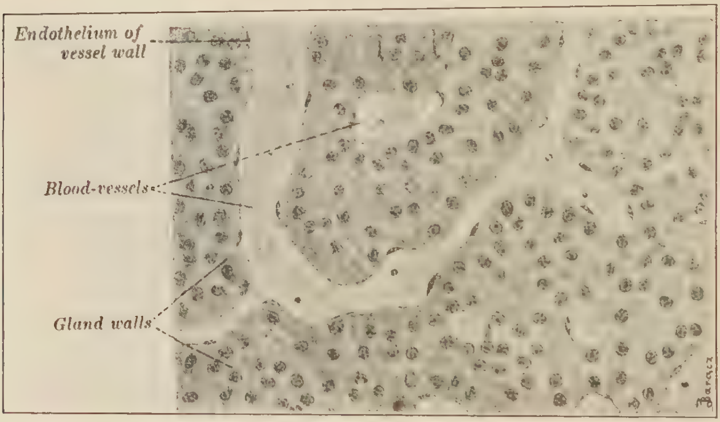

FIG. 30.—From section of hypophysis cerebri (anterior lobe) of dog. (Szymonowicz.)

F. Tilney[2] described more exactly the grouping of the epithelial cells in the pars intermedia of Herring. Tilney thought the parts of the pars intermedia surrounding the stalk and actually in or on the lower wall of the third ventricle should be called by reason of situation and anatomical structure a separate part, *pars tuberalis.*

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[1] Loc. cit., p. 160.

[2] Internat. Monatschr. f. Anat. u. Physiol., 1913–1914, **30**, 258.

The figures adjacent (ox gland) from Atwell and Marinus[1] make the subject clearer (Figs. 31, 32 and 33). The pars tuberalis and included neural stalk can evidently not be entirely removed without destroying important nervous structures. The pars tuberalis contains peculiar acinous cells (see figures), which have no pressor content.[2] The pars tuberalis is possibly accessory to the anterior lobe;[3] or possibly subserves special functions.

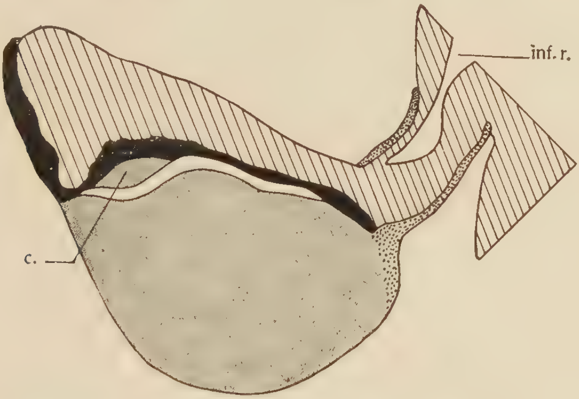

FIG. 31.—Diagrammatic mesial sagittal section of bovine hypophysis, nasal end at the right. × 4. *Lined*, neural lobe, neural stalk and brain wall; *black*, pars intermedia; *fine stipple*, pars anterior propria; *coarse stipple*, pars tuberalis; *inf. r.*, infundibular recess; *c*, cone of Wulzen. (Atwell and Marinus.)

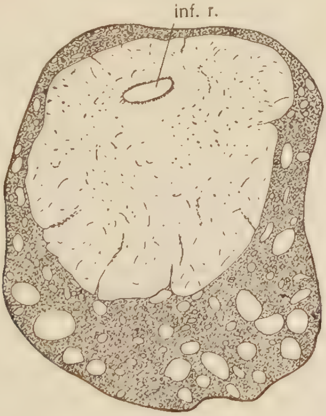

FIG. 32.—Cross-section of pituitary stalk (ox). × 20. Neural stalk (light) is in center, and is surrounded by the pars tuberalis which shows numerous bloodvessels; *inf. r.*, infundibular recess. (Atwell and Marinus.)

[1] Am. Jour. Physiol., 1918–1919, **47**, 76.

[2] Atwell and Marinus: Loc. cit.

[3] Abel, J. J.: Loc. cit., p. 161.

The *pars nervosa* does not appear to contain anything but glia cells and neuroglia and ependymal fibers (Herring). In the interstices of the pars nervosa and among the cells of the pars intermedia are to be found certain rounded structureless hyaline or

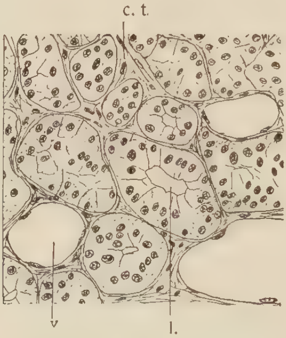

FIG. 33.—Section of pars tuberalis of hypophysis (ox). × 300. *l*, lumen of an acinus distended by small granules; *c.t.*, connective tissue; *v.*, small vessel. (Atwell and Marinus.)

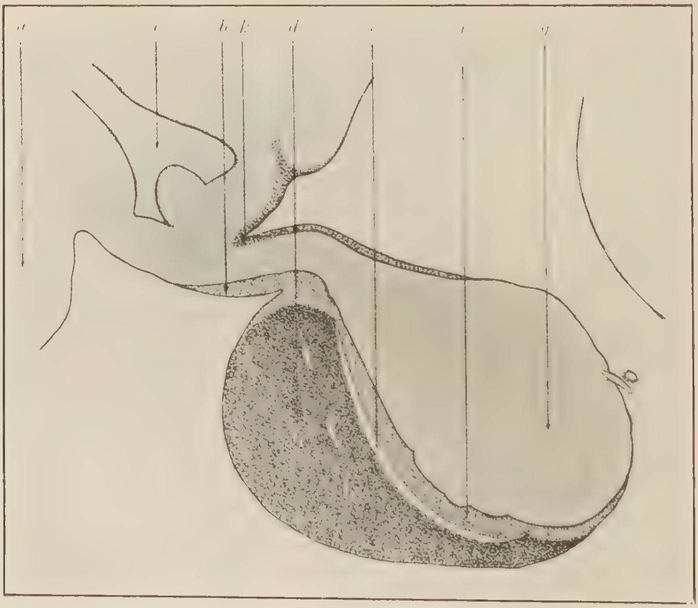

FIG. 34.—Mesial sagittal section of pituitary of adult monkey. *a*, optic chiasm; *b*, tongue-like process of pars intermedia (pars tuberalis of later writers); *c*, third ventricle; *d*, anterior lobe proper; *e*, epithelial cleft; *g*, nervous substance of posterior lobe; *i*, epithelial investment of posterior lobe; *k*, epithelium of pars intermedia (pars tuberalis), extending over and into adjacent brain substance. (Herring.)

faintly staining masses, called in the microscopical sense "colloid." They are variously supposed to be of secretory origin, or due to cellular degeneration. The nervous lobe and neural stalk both have a pressor content. Whether this originates in the pars nervosa or is derived from the pars intermedia, which also has a pressor content, is unsettled. Bailey and Bremer's claim (p. 165) is by no means justified by the literature.

Nerves.—The nerves of the pituitary gland have been studied in dogs and cats by W. E. Dandy.[1] Dandy failed to find a parasympathetic supply, and concluded as follows: "The nerve supply is from the carotid plexus of the sympathetic. The anterior lobe has an abundant supply; the posterior lobe a very scanty one. The pars intermedia receives its nerves from the stalk." He hesitated to differentiate positively between the secretory and vasomotor function of these nerves, but gives reasons for deciding them all secretory.

Weed, Cushing and Jacobson[2] found that stimulation of the fibers reaching the pituitary *via* the superior cervical sympathetic ganglia caused glycogenolysis and glycosuria (probably influencing the pars intermedia in this regard) which is due to liberation of a chemical substance and is independent of any possible nervous impulse.

Blood Supply.—Dandy and Goetsch[3] have studied the blood supply of the dog's pituitary. The anterior lobe is abundantly supplied by many small vessels from the inner margin of the circle of Willis. These vessels converge to the stalk. It therefore appears that section or ligation of the stalk will endanger the circulation of the anterior lobe. The pars intermedia is fed by vessels from the stalk, from the brain and from the posterior gland. The posterior gland is supplied by branches from the internal carotid.

Development. The anterior gland first appears in the embryo as an infolding or pouching of the nasopharyngeal mucous membrane, called long ago, after the discoverer, *Rathke's pouch*.[4] The distal end of the lumen of the pouch is persistent through life as a blind slit.

The nervous part of the posterior pituitary is a downward growth from the brain; it meets and fuses with the upper posterior part of Rathke's pouch, ultimately forming the neural infundibulum and the pars nervosa of the posterior lobe.

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[1] Am. Jour. Anat., 1913–1914, **15**, 333.

[2] Bull. Johns Hopkins Hosp., 1913, **24**, 40.

[3] Am. Jour. Anat., 1910–1911, **11**, 137.

[4] Rathke, H.: Arch. f. Anat. u. Physiol., 1838–1839.

Accessory Pituitary Glands.—The sella is said to contain at times some minute discrete epithelial bodies apparently developing independently from separated bits of the fetal anlage (Rathke's pouch).[1] Dandy and Goetsch[2] have described on the floor of the dog's sella a *parahypophysis* embedded in the dura, which is possibly of the same nature.

The *pharyngeal hypophysis* (*Rachendachhypophyse* of German writers) is really only the atrophic remnant of Rathke's diverticulum, marking the site of the original fetal bud. Its survival is comparable to the survival at the root of the tongue of the thyroglossal duct. The pharyngeal hypophysis is a minute body in the mucous membrane of the roof of the pharynx close to the upper edge of the nasal septum. W. Haberfeld[3] has found it as large as 5½ by 9 mm. He thinks it may sometimes contain viable rests of pituitary tissue. Minute epithelial rests are said to be found, also, on the stalk and neighboring regions of the pituitary; they may at times form the starting-point of tumors.

Hypophysis in Other Animals.—The comparative anatomy of the gland has been intensively studied. It is present in frogs, reptiles, birds and all mammals.[4] In the dog it is much more easily gotten at by operation than in man, as it is much less closely invested by osteofibrous coverings. An excellent account of the gross structure and the histology of the gland (with copious references to date) in the cat, dog, monkey, man, ox, pig and rabbit is to be found in the paper by P. T. Herring.[5] Elaborate studies in the *comparative anatomy* and *embryology* of the pituitary may be found in a paper by F. Tilney,[6] and a series of papers by P. T. Herring.[7] Some excellent original illustrations of sections of the pituitary gland in various animals have been prepared by W. Blair Bell.[8]

PHYSIOLOGY OF THE PITUITARY GLAND.

For the pituitary gland as well as for other strange organs there was an age of guesswork. Galen is said to have conceived the idea that the pituitary body is a filter; that it filters into the pharynx the cerebrospinal *pituita* or moisture. In the seventeenth century Piccolhomini suggested that the pituitary body closes the infundibulum and prevents the escape from the body of the "vital spirits." Early in the seventeenth century Descartes placed the pituitary gland at the anterior angle of the parallelogram of which the center, the pineal gland, is the seat of the soul. Later writers thought it a sort of lymph follicle (Monro, Boerhaave, Sylvius). Other quaint fancies may be found in Paulesco's account of the gland.[1]

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[1] Cowdry, C. V.: Barker's System.

[2] Loc. cit., p. 159.

[3] Ziegler's Beiträge, 1909, **46**, 133; with literature.

[4] Paulesco: Loc. cit., p. 161.

[5] Quart. Jour. Exp. Physiol., 1908, **1**, 121.

[6] Mem. Wistar Inst. Anat. and Biol., Philadelphia, 1911.

[7] Quart. Jour. Exp. Physiol., 1908–1914.

[8] The Pituitary, New York, Wm. Wood & Co., 1919.

The period of guesswork was slowly followed by the period of pathological facts and experiments, but the physiology of the gland is still a subject of great difficulty, and many points remain entirely undecided.

A brief review of the literature of pituitary physiology would far exceed the limits of this volume. Many of the older contributions have only a historic value. References for important papers of earlier date may be found in the first edition of S. Vincent's[2] volume, in Paulesco's[3] monograph and in the study by Harvey Cushing.[4] J. J. Abel's "Harvey Lecture"[5] is recent, and of great value and interest for the posterior lobe; Herbert M. Evans's "Harvey Lecture" (anterior lobe) is not yet in print.

For purposes of convenient study a somewhat artificial and overlapping classification of the known facts follows:

1. **Clinical and Autopsy Records of Disease in Man.**—These are set out fully in following sections; here only a summary is needed.

For the first stories of pituitary disease in man we must go back to 1886, when Pierre Marie[6] published his original accounts of a new disease, which he called *acromegalie*. In 2 patients of his own and several more from the literature he described a train of quite uniform symptoms depending essentially upon an increase in size of the bones and soft tissues of the head and extremities. Many other characteristic appearances were noted (p. 180). In the next year O. Minkowski[7] reported a case of his own, and collated others, and was the first to remark that the patients showed a remarkable increase in the size of the pituitary body. The increase seemed to be very generally due to hyperplasia or adenoma. Marie's paper attracted an immense amount of attention; the literature grew fast; in a few years his observations had been everywhere confirmed. In growing children acromegaly was found to be associated with gigantism. Marie himself supposed that the pituitary lesion caused a deficiency of secretion. Subsequent writers have concluded, with some degree of probability, that the anterior gland is in a state (often only temporary) of oversecretion (hyperpituitarism).

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[1] Hypophyse du cerveau, Paris, Vigot Frères, 1908.

[2] Loc. cit.

[3] Loc. cit.

[4] Pituitary Body and Its Disorders, Philadelphia, Lippincott, 1912.

[5] Bull. John Hopkins Hosp., October, 1924.

[6] Rev. d. méd., 1886, **6**, 297.

[7] Berl. klin. Wchnschr., 1887, p. 371.

The clinical and pathological evidence does not all point one way. Some autopsies on acromegaly have been reported in which the pituitary was negative; some pituitary tumors have been found in which acromegaly was absent. To most students it has seemed possible, however, from analogies in the thyroid gland, to reconcile these data to one another. In glands microscopically negative circulatory and chemical changes are still possible; and tumors other than cellular hyperplasias and adenomas might be expected to be destructive or negative in their glandular effects rather than stimulative.

Fifteen years later A. Froelich[1] first described in man cases of a curious disease marked by atrophy of the genitals and a notable increase in the body fat. Autopsies in this disease (*adiposogenital dystrophy*, the Froelich syndrome) have frequently shown destructive or pressure lesions of the pituitary, both anterior and posterior lobes (p. 190).

The interesting and remarkable phenomena of *Simmonds' disease* (p. 202), which appears to be a cachexia associated always with destructive lesions in or around the pituitary, have also a place in physiological studies.

Finally, the disease called *diabetes insipidus*, known for years past as a clinical entity, has been found to be relieved entirely for a few hours by injections of suitable doses of posterior lobe extract. That this is not a purely pharmacological effect is indicated by the additional facts that autopsies on such patients have shown macroscopical lesions of the pituitary or its neighborhood in a significant number of cases, and that experimental operations in and around the sella will often cause a polyuria of the same general character.

2. **Operative Experiments in Animals.** Work of this kind involves many difficulties. The technical skill required is obviously unusual. Danger of infection is great. The neural stalk and pars tuberalis cannot be removed without damaging important structures in the brain. Lesions of the tuber cinereum itself involve possible damage

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[1] Wien. klin. Rundsch., 1901, **15**, 883.

to the gland or its circulation. Results might therefore be expected to be perplexing and conflicting, as they have actually proved to be. But a brief review is instructive, and in many ways confirmatory of other lines of study.

N. C. Paulesco,[1] of the University of Bucharest, after a review of the negative or conflicting experiments done prior to his own time, reported that in dogs "complete removal" of the gland (*i. e.*, of the intrasellar portion) by the temporal route is soon followed by collapse, coma and death. Realizing that the operation is a capital one, and allowance must be made for accidental damage to vital structures, he did control operations on other dogs, the control work being similar except for actual removal of the glands. To insure the completeness of his hypophysectomies he made serial sections of the residual contents of the sella after death of the dogs. The fatal result seemed quite certainly in causal relationship with the complete removal of the pituitary body. His conclusions were more fully as follows:

"Total hypophysectomy is followed after a brief delay by the death of the animal.

"In dogs the mean duration of survival is twenty-four hours. When more time than this elapses it is because some remnants of the gland have been left behind.

"No particular and characteristic symptom is evinced by this acute insufficiency of the hypophysis.

"When the anesthetic wears off the animal behaves like the controls. The temperature, lowered during narcosis, rises and reaches normal, but soon commences to drop again. The animal, which at first gets up, walks (without paralysis or convulsions) and drinks milk, slowly collapses, passes into coma and quickly succumbs."

He found that after partial hypophysectomy the duration of postoperative life seemed proportional to the amount of viable gland left behind in the sella. In animals surviving even five months to a year he was unable to notice any changes in the head (*museau*) or limbs. (This was in reference to Marie's view that acromegaly ought to result.)

Observations by Paulesco and by other experimenters of the same period added the facts that the subject animal may have fibrillary twitching of the muscles, arching of the back and insensitiveness to stimuli before final exitus. This condition was called *cachexia hypophyseopriva acuta*. The onset of acute symptoms appeared to be associated with the removal of the anterior rather than posterior lobe.

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[1] Loc. cit., p. 161.

The researches of H. Cushing and his associates, Reford, Crowe, Homans and Goetsch, at Johns Hopkins Hospital,[1] seem to have experimentally confirmed in every essential way the work of Paulesco. They very fairly considered data offered by assailants of the doctrine, and added many remarkable and original facts: "In the course of their experiments, which have comprised more than 200 hypophysectomies, it was observed that puppies survived a total extirpation longer than did adults (adults, three to five days; puppies, ten to thirty days), possibly due to greater functional adaptability in early life of some accessory glandule, such as the Rachendachhypophyse of Erdheim or the dural parahypophysis of Goetsch and Dandy. It was found that life could be prolonged (spared?) by immediate transplantation of the removed gland; that in all recovered cases, in agreement with Paulesco, a viable fragment of anterior lobe was invariably present; that animals with a remnant of pars anterior temporarily insufficient to support life could be tided over a threatening period of cachexia hypophyseopriva by injection or ingestion of anterior lobe extract; and that removal of the posterior lobe alone led to no definitely recognizable symptoms, it being fully realized that a fragment of pars intermedia was inevitably left adherent to the stalk even in the most complete extirpations."

Cushing recognized that complete removal of the posterior lobe (including what is now called neural stalk and pars tuberalis) in higher mammals is impossible. He extended his work by doing a partial removal of both lobes. When a large part of the anterior lobe was removed (leaving enough to save life, as he supposed) and the posterior lobe was cut away close to the stalk, it was found that the animal (Figs. 35 and 36), while surviving indefinitely, gets fat, greatly increased carbohydrate tolerance being shown by numerous experiments; it has a subnormal temperature, a diminished blood-pressure and develops a partial sexual involution, or if a puppy, fails to develop the sex glands. Atrophic changes in the skin and hair also occur. Sometimes the quantity of urine is greatly increased (diabetes insipidus). In puppies the intelligence is clouded. Growth of the long bones in one instance was retarded. The condition was evidently an experimental reproduction of the phenomena of Froelich's disease.

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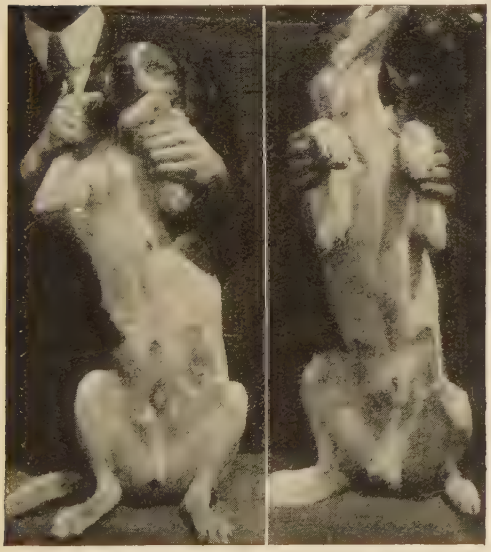
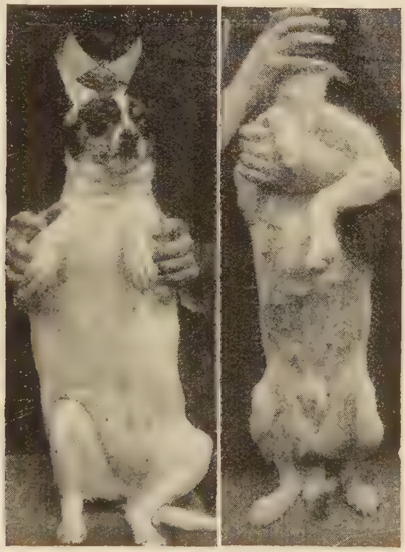
[1] Cushing, H.: Loc. cit., p. 161.

Cushing's conclusions were accepted by the profession with general approval. Experiments by Biedl[1] and by Aschner[2] appeared to confirm them. But in 1913 Camus and Roussy[3] claimed that similar effects (polyuria and adiposogenital dystrophy) could be got by experimental lesions of the tuber cinereum, or more generally of the floor of the third ventricle (hypothalamus), which they punctured through the body of the sphenoid with a heated drill. In the same journal[4] they claimed to have produced polyuria by a lesion of the hypothalamus in an animal previously deprived of its hypophysis without permanent polyuria.



A *B*

Fig. 35



C *D*

Fig. 36

Fig. 35.—Hypopituitarism in adult male dog. *a*, beginning adiposity and testis atrophy; *b*, control. (Cushing.)

Fig. 36.—Hypopituitarism in female adult dog. *c*, marked adiposity after partial extirpation; *d*, control. (Cushing.)

Bailey and Bremer[5] have further reopened the entire question of pituitary function by positively asserting that diabetes insipidus and the Froelich syndrome may be all produced in dogs by minute lesions of the tuber cinereum, *post mortem* serial sections of the pituitary gland showing everything in the sella normal. They also declare that we have no valid evidence of either hypo- or hypersecretory functions in the hypophysis, and that the etiology of acromegalia and gigantism is still unresolved.

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[1] Loc. cit.

[2] Wien. klin. Wchnschr., 1910, **32**, 572; Pflüger's Arch., 1912, **146**, 1.

[3] Compt. rend. soc. d. biol., 1913, **75**, 483, 628.

[4] Ibid., 1920, **83**, 1578.

[5] Arch. Int. Med., 1921, **28**, 773.

In respect of their conclusions about acromegaly they offer no experimental evidence, but bend to their purpose all the facts and hypotheses of the literature—some of them already many years old—which speak against the pituitary relationship. That portion of the pituitary theory is therefore where it was before.

Their conclusions as to diabetes insipidus and adiposogenital dystrophy are based upon temporal operations done on about 18 dogs. Various small knife lesions were made in the tuber cinereum around the infundibulum. The pituitary gland and stalk were spared.

As usual, a study of the protocols gives one the impression that the conclusions have been rather hastily drawn. The authors' manner of disposing of the larger difficulties in their way may be illustrated by the following paragraph (*brackets mine*):

"As to the function of the posterior lobe, the experimental evidence is unequivocal. Its removal causes no symptoms [but it cannot be entirely removed, see p. 164]. Moreover, its structure is non-glandular [but it is intimately in contact below with the pars intermedia and above with the pars tuberalis]. Camus and Roussy are quite justified in speaking of it as an atrophied nervous lobe [but who can prove this?]. We must reckon with the fact that from it can be extracted a very active substance, pituitrin; the origin of pituitrin in the posterior lobe and not in the pars infundibularis we accept as an established fact [but is still very much in doubt]. It is difficult to conceive that such a substance, which is found in the pars nervosa of all vertebrates, should be without significance. Since the pars nervosa is composed almost wholly of glia, it is quite possible that this material may be extracted from the glia anywhere [but Abel[1] found it entirely absent from a tumor composed entirely of glia]."

P. Bailey alone[2] reviews the literature in support of the same contentions. He summarizes his previous work, and suggests that lesions of the tuber cinereum produce their effect by injuring nerve centers in the hypothalmic region which control metabolism, sex development and urinary water.

These observations have come somewhat as a shock to the believers in the older hypothesis. Cushing[3] seems to preserve an open mind, still apparently inclining to the older view. J. J. Abel[1] thinks there is not much question that Camus and Roussy, and Bailey and Bremer are in error. He notes the nearly complete confirmation of the older hypothesis by the recent work in Amphibia (below), and thinks that removal of the sellar gland may be compensated for possibly by the presence of a growth hormone in the pars tuberalis in many of the experimental animals; while it is hard to suppose that any lesion of the tuber cinereum certainly fails of damage to the stalk and the circulation in the sella.

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[1] Loc. cit.

[2] Ergbn. d. Physiol., 1922, **20**, 162.

[3] Jour. Am. Med. Assn., 1921, **76**, 1721.

Meanwhile much interesting operative work continues to appear. G. M. Curtis[2] has repeated the puncture experiments of Bailey and Bremer on dogs (number not stated). Five had "transient," 1 had a five months' polyuria. Pituitrin relieved it. Autopsy on the severe case showed a small cyst near the pituitary stalk. A. J. Walton[3] claimed a "total extirpation" of the pituitary with recovery and "progress" in 2 human subjects.

Smith and Graeser[4] injected chromic acid into the hypophysis of 16 rats. Resulting disturbances ranged from slight sex impairment to Frœlich's syndrome. In only 1 case microscopical examination showed that the hypothalamus was unquestionably injured. Injections of anterior hypophysis successfully reëstablished the ovarian cycle in 3 cases (which had no adiposity). After full development of adiposogenital dystrophy injections were ineffective.

Dott[5] cut the stalk and inserted a bit of platinum close to the pars posterior of the hypophysis in dogs and noticed afterward an immense polyuria. He considered it a hypersecretory effect. But this is by no means evident; the irritation might as well be inhibitory, which would make this experiment fit exactly with other facts.[6]

For the story of *excision effects in Amphibia* there is not much space. Abel[7] mentions many of the newer references. The subject has been eagerly studied, and with many curious and interesting results. The removal of the anterior lobe of the hypophysis in frogs in quite possible *in toto.* Removal is not fatal, but retards growth and metamorphosis. Removal of the posterior lobe is also possible without danger to life. A curious and noticeable effect that has no counterpart in the mammals is the cutaneous pallor that follows excision of the posterior lobe ("albino frog"). This is found due to contraction of the melanophores. Dark color can be restored by adding to the water a small amount of the solution of posterior lobe of hypophysis of any common animal, like the ox.

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[1] Loc. cit.

[2] Anat. Record, 1924, **27**, 201.

[3] Brit. Med. Jour., November, 1922, p. 835.

[4] Anat. Record, 1924, vol. **27**.

[5] Quar. Jour. Exp. Physiol., 1922-1923, **13**, 241.

[6] Abel, J. J.: Loc. cit.

[7] Loc. cit.

3. **Gland Transplantations.**—In tadpoles (*Rana pipiens*) deprived of their pituitary gland by operation (removal of the buccal anlage) B. M. Allen[1] has reported several hundred tests in which the subjects were supplied with a new gland by subcutaneous implantation of adult pituitary tissue. The subjects grew and metamorphosed faster than the controls. Successful isotransplantations by Cushing in dogs seemed to save life at times; also in 1 human case homoioplasty (gland from a new-born baby) seemed to be distinctly helpful.

4. **Injection and Feeding Experiments.**—A large amount of work has been done along this line of investigation. With the best intentions the workers have had to labor under the handicap of not knowing the strength of dose necessary, nor whether oral administration or cœlomic introduction is necessary for the successful action of anterior lobe extracts. What with the use of different animals, different gland extracts, different doses, different methods of administration, insufficient controls and insufficient subjects, the published results have had a wide range of success and failure, and are not fairly comparable with one another. For example, I. Kross[2] reviews pessimistically the recent literature of pituitary gland feeding, and reports his own experiments as indecisive of, or against the influence of anterior lobe injections as a developer of sex organs in animals. On the contrary, Evans and Long[3] injected anterior lobe of bullocks' hypophysis into female rats, and noticed greatly increased growth of fat and slightly increased growth of the bones—a mild degree of gigantism. In the very large ovaries lutein tissue was abundant, but there were no ripe follicles, and œstrus appeared never to occur. E. Uhlenhuth[4] fed a series of young salamanders on anterior lobe and a series of controls on earth worms. The subjects rapidly outgrew the controls; as compared with the averages of the species some were giants. L. Hogben,[5] working with axolotl larvæ (*Amblystoma trigrinum*) found feeding anterior lobe inefficient, but injection of the same substance caused rapid metamorphosis, even apparently in thyroidless animals.

5. **Chemical Studies.**—Up to the present writing no reports have been confirmed as to the active principle, or principles of the

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[1] Science, 1920, **52**, 274.

[2] Am. Jour. Obst. and Gynec., 1922, **4**, 19.

[3] Anat. Record, 1922, **23**, 19.

[4] Jour. Gen. Physiol., 1920–1921, **3**, 347.

[5] Proc. Roy. Soc. London, 1922–1923, **94**, 204.

anterior lobe. T. B. Robertson[1] affirmed that a lipoid of therapeutic value could be extracted from the anterior lobe. He called this product *tethelin.* Subsequent students have questioned both his laboratory processes and the value of the product. Drummond and Cannan[2] found tethelin to be a mixture of lipoids, and failed to note any effect on the growth of mice by its administration. P. E. Smith,[3] working with the filter residues of Robertson's experiments got more striking results than from tethelin. Robertson has rejoined that Smith's technique was faulty. So far as I am informed, there the question now stands.

The *posterior lobe* contains a substance, or several substances, which have a marked and varied physiological and pharmacological effect. The various names the extract goes by will be mentioned in a later section. Here we will call it simply *postlobe extract.*

The origin of postlobe extract is either in the cells of the pars intermedia or in the pars nervosa, or both. It is also present in the neural core of the infundibulum, and (Abel) in the tissues of the hypothalamus (sheep) around the stalk. It is absent from the anterior lobe (all authors) and from the pars tuberalis (Atwell and Marinus[4]). It was absent from the tissues of a glia tumor (Abel). It is absent from all other brain tissues (Howell). Never having been gotten in absolutely pure condition, it is possible that some of its properties are due to contamination, for example, with the depressor substance or substances common to so many of the mammalian organs, and also found in the brain. But in essentials the postlobe extract has been found to have, in the hands of a multitude of students, a very uniform action.

Pharmacologically it is: (*a*) A powerful stimulant of smooth muscle, actively of the intestine, tremendously of the uterine muscle; it is the most reliable of all oxytocics. (*b*) It is a pressor principle, more persistent than epinephrine, and acting synergically with it. (*c*) It is a diuretic in "green-fed rabbits" (Abel) and an antidiuretic in diabetes insipidus; it was recommended first as a treatment for this disease by von den Velden.[5] (*d*) Injected in animals it produces a condition of Cheyne-Stokes breathing in effect, that is, periods of hurried breathing alternating with apnea. (*e*) It produces glycosuria in rabbits when injected in large doses (Borchardt[6]), but dogs are more refractory. (*f*) Finally, it blackens albino frogs. This last property has also been the subject of numberless speculations and experiments. The general subject of the effect of drugs upon melanophores of the pigmented skin of Amphibia had a literature of more than 150 papers some fifteen years ago (Hogben and Winton[1]), and the list is still growing. One can only mention here that in causing expansion of melanophores postlobe extract acts in opposition to adrenalin and to pineal extract, both of which *bleach* black frogs—adrenalin very actively (p. 221). Huxley and Hogben[2] and Hogben and Winton[3] found that β-iminazolylethylamine (histamin), though it has various other properties of postlobe extract, does *not* expand melanophores.

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[1] Jour. Biol. Chem., 1916.

[2] Biochem. Jour., 1922, **16**, 53.

[3] Abel, loc. cit.

[4] Loc. cit., p. 157.

[5] Berlin. klin. Wchnschr., 1913, **50**, **2**, 2083.

[6] Ztschr. f. klin. Med., 1908, **66**, 332.

The supposed *galactogogue* effect of postlobe extract is generally now attributed only to its contractile influence on the smooth muscle of the milk ducts.

As in the case of epinephrine here also one must carefully remember that all these effects are *primarily pharmacological;* how many of them the extract actually produces in the everyday work of the body is a matter for very cautious inference.

For the history and literature of this remarkable substance the large works on pharmacology must be consulted. It was discovered by W. H. Howell,[4] and almost at the same time by Czybulski. Howell's controls were carefully made, and he stated that neither the anterior pituitary nor any other part of the contents of the skull would give any such reaction. He noted that while the pressor effect on heart and vessels was comparable to that of adrenal extracts, it was more persistent. Hammett's article[5] gives useful references. J. J. Abel[6] brings the literature largely to date, and expresses the opinion that the posterior lobe contains but one principle. He gives the chemical process by which it can be separated as tartrate ("pituitary tartrate") in almost pure condition and with a very powerful oxytocic, antidiuretic, cardiovascular and respiratory effect. Its chemical formula and affinities are at present conjectural.

The *usual organ proteins* are abundant in the pituitary. Their physiological action has not been studied to any great extent.

Iodine. Traces of iodine found in beef pituitary (Kendall, Henderson, quoted by E. R. and M. M. Hoskins[7]) are probably not greater than those occurring in mammalian muscle, liver and brain. H. Gideon Wells[8] thinks that traces found in human glands are attributable to the frequent treatment of hospital patients with iodine and its compounds, but considers that wider investigation should be made before the question is considered answered.

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[1] Proc. Roy. Soc. London, 1922–1923, **94**, 151.

[2] Proc. Roy. Soc., London, Series B, 1922, **93**, 36.

[3] Ibid., 318.

[4] Jour. Exper. Med., 1898, **3**, 245.

[5] Barker's System, vol. **1**, 749.

[6] Bull. Johns Hopkins Hosp., 1924, **35**, 305.

[7] Endocrinology, 1920, **4**, 1.

[8] Jour. Biol. Chem., 1909, **7**, 259, with literature.

6. **Therapeutic Results.**—Owing to the difficulties incident upon the preparation of reliable and standardized extracts of the whole gland, and of its lobes, and the imperfect knowledge as to whether extracts given *per os* are absorbed quantitatively and without modification, therapeutic successes and failures are only a secondary source of physiological information. As possibly only pharmacological effects they are to be interpreted with reserve. So far as they may be trusted, they are informative and helpful. Full details are to be found in later sections of this chapter. Here only a summary is needed.

Cushing[1] reported that juices of the whole gland and of its several portions, extracted with a Buchner press and given *per os*, had the theoretically anticipated physiological effects on subject animals. Boiled extracts of anterior lobe injected into animals with the lowered temperature of hypophyseal cachexia would cause a rise of temperature. Blanks with extracts of other glands failed. Blanks with anterior hypophysis extract on normal dogs had no effect on temperature.

Suitable opotherapy in Froelich's syndrome, Simmonds' disease, and diabetes insipidus has had a fair measure of clinical success. Undersized children with shallow sellas, not growing under other methods of treatment, have begun to grow after the administration of anterior gland. Anterior gland seems to relieve those cases of "pituitary headache" in which the diagnosis has been clinically assured.

7. **Critical Summary.**—The facts assembled under the previous heads are of great complexity. Their satisfactory causal coördination is at present conjectural. In general, it seems to be proved for many vertebrates that destructive or irritative lesions to or in the neighborhood of the pituitary gland may interfere with growth, retard sex development, delay carbohydrate metabolism, reduce temperature, bleach the skin (of frogs), cause polyuria and induce the symptoms of Simmonds' disease. Whether in mammals life can be maintained after the removal of the intrasellar part of the gland is disputed. Frogs can live without the whole gland, or either of its parts.

Through Cushing's time it seemed possible to correlate the growth hormone and the sex adjuvant with the anterior lobe. If we accept the facts (but not the conclusions) of the work by Camus

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[1] Loc. cit.

Roussy, and Bailey and Bremer, we can still suppose with Abel that in mammals the pars tuberalis, which contains no pituitrin, acts as an accessory anterior gland. At all events recent researches seem fairly to prove, in the case of the Amphibia, that the anterior gland actually does control growth and metamorphosis. If there be a separate "temperature hormone" anywhere its site of origin is doubtful. The control of carbohydrate metabolism is generally assigned to the posterior lobe perhaps the pars intermedia, if we may trust to the indications of the experiments by Weed, Cushing and Jacobson,[1] which produced glycosuria in dogs. The output of urinary water (possibly the carbohydrate metabolism also) is influenced by postlobe extract, which is found in the pars intermedia, the pars nervosa, the neural core of the stalk and the parts of the brain adjacent to the neural core. Why polyuria is sometimes a separate clinical entity is obscure. If in mammals removal of the intrasellar anterior gland *and of the pars tuberalis* possibly causes death the chemical reasons are entirely unexplained.

As an alternative to this view we are offered the claim of Bailey and Bremer, that the pituitary is an atrophic, functionless body not essential to life, that the cause of acromegaly and gigantism is unknown, that polyuria and adiposogenital dystrophy are due to damage to certain hypothetic nerve centers in the hypothalamus and that the association of destructive lesions of the pituitary gland with Simmonds' disease is an accident. The older conclusions seem less beset with difficulties; but a final decision awaits further research.

Therapeutic results have a certain value. They are all confirmatory of the older view.

I have avoided the discussion of *pituitary glycosuria* at any length because of the obscurity of the whole question. Very large injections of postlobe extract have been mentioned (p. 169) as a cause of glycosuria. Certain diseases of the pituitary (acromegaly for example) are sometimes associated in their early stages with glycosuria, and later on with absence of sugar in the urine and with increase in weight. This might be explained as an irritative hypersecretion of the same hormone whose later lack induces obesity. Puncture lesions of various parts of the base of the brain (especially of the floor of the fourth ventricle, "piqûre") also produce glycosuria. Even blows on the head may produce glycosuria. This subject awaits further investigation.

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[1] Loc. cit., p. 159.

The experimental production of gigantism by feeding or injection of anterior pituitary extracts would be of great significance. The work of Hogben, Uhlenhuth and Evans and Long (p. 168) is suggestive, but not so far convincing. The failures may be repaired by better attention to technique and dosage. Such studies are now going forward with speed and enthusiasm.

Physiological Epochs.—Some other points in the physiology of the pituitary require brief mention. At the *menstrual period* the gland is said to be enlarged, undergoing not only engorgement of its vessels, but increase in the cellular parenchyma. In this regard it is thought to act as the thyroid does.

Erdheim and Stumme[1] made a laborious study of the *gland in pregnancy* as compared with the gland in non-pregnant women. They found in the glands of pregnancy an increase in weight and a notable change in the proportions of the various cells. They studied an immense number of autopsies. In pregnancy the eosinophile and basophile cells were pushed away into corners by an immense increase in the chief cells ("Schwangerschaftszellen"); the weight of the entire gland was increased from 0.6 or 0.7 to 1.1 and 1.2 gm.

Hibernation.—Some early observations on hibernating animals by Cushing and his associates led them to the belief that during that period there is a functional involution of the pituitary, which enlarges again and becomes more vascular when the animal awakes. Later writers suggested that this change is a consequence rather than a cause of hibernation, and Rasmussen's studies[2] on 32 woodchucks entirely confuted the hibernation theory. But it is still joyously cherished by a great number of popular writers, and by many physicians who fail to keep up with the literature.

Basal Metabolism in Pituitary Disease.—The most extensive data have been collected by Boothby and Sandiford.[3] Of 30 cases of acromegaly the majority were within 15 per cent of the normal average. One was below normal; 8 were 20 per cent and more above. Some of the latter possibly had a complicating hyperthyroidism. In 58 cases of hypopituitarism about one-third showed a distinct depression. Students especially interested will find further data and references in the books by E. M. Du Bois[4] and by John T. King, Jr.[5]

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[1] Ziegler's Beiträge, 1909, **46**, 1.

[2] Endocrinology, 1921, **5**, 33.

[3] Jour. Biol. Chem., 1922, **54**, 783.

[4] Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1924.

[5] Basal Metabolism, Baltimore, Williams & Wilkins Co., 1924.

DISEASES OF THE PITUITARY GLAND.

The diseases to which the pituitary gland is subject are manifold. Their pathology and symptoms are often confusing, and many doubtful points arise on every hand, which, in the lack of decisive objective data, have been too often decided on *a priori* grounds appealing to the fancy or judgment of the clinician. At the present time no classification of these disorders can be other than artificial. Some diseases seem to limit themselves to a crippling of the posterior lobe only, *e. g.*, polyuria; some involve one lobe first and the other afterward; some evidently involve both lobes from the beginning of the trouble.

For purposes of orderly description perhaps as good an arrangement as any is to treat first of *inflammations* and *degenerations* of the entire gland and its neighborhood; then of *tumors;* then of *secretory disorders.* But there are many patients in whom one or several or many of these conditions may concur, or may follow upon one another.

INFLAMMATIONS OF THE PITUITARY GLAND.

Among the chronic inflammations **tuberculosis** and **gumma** are to be mentioned. These may be parts of a general infection, in which the diagnosis will depend on general considerations, and the treatment will be that of the primary condition. T. W. Letchworth[1] has described a case of polyuria and one-eye blindness in a boy, aged sixteen years. Autopsy showed a tuberculoma surrounding the pituitary body, chiasm, optic nerves and tracts. Luetic meningitis in the interpeduncular region is thought to be an occasional cause of diabetes insipidus, and will be considered at length in a later section. M. Simmonds[2] reported 13 cases (autopsy findings) of pus embolism or of infarction of the pituitary body, affecting various parts of the gland, and attended with more or less destruction of the parenchyma. He called attention to this pathological confirmation of the anatomical studies of the blood supply of the gland (p. 159), indicating that the arteries of the anterior lobe are terminal arteries carried in the stalk.

General Acute Infections.—It seems more than an accident that a fair percentage of pituitary disorders of secretion date from typhoid and other general infections. Cushing[3] thinks it "evident" in 1 of his cases that skeletal overgrowth followed an attack of typhoid and pneumonia at the age of fourteen years; and he mentions the general impression among observant physicians that after typhoid in growing boys and girls "a notable augmentation of skeletal growth may occur." Langdon Brown[1] quotes an account by C. H. Miller of a young officer under treatment for diabetes insipidus, who had also a thrombosis of the saphenous vein. The patient had had "some pyrexial attack" at Saloniki previously. He proved to be a paratyphoid carrier. His Wassermann was negative. The virus of epidemic encephalitis is believed to be also an occasional cause of destructive lesions in or around the pituitary body.

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[1] Brit. Med. Jour., 1924, **1**, 1127.

[2] Virchow's Arch. f. path. Anat., 1914, **217**, 226.

[3] Loc. cit., p. 236. (P. 161 of this book.)

The frequency of hyperthyroidism after acute infectious diseases like influenza is somewhat analogical. Exact proofs are lacking, but the conjecture comes with reasonable scientific limits.

Arterial Disease in the cerebral vessels, especially when localized in the circle of Willis, may interfere with the nutrition and function of the pituitary. Parasyphilitic endarteritis is particularly to be borne in mind.

Degenerations.—Fatty and amyloid changes doubtless affect the pituitary gland when widely present elsewhere throughout the body. They are of no known clinical importance. *Calcification* is a more interesting and practical matter. The causes of this phenomenon are more or less theoretical, but a recent report by Pfahler and Pitfield[2] seems to prove that the condition may be of clinical importance. These authors based the diagnosis on the appearance in profile roentgen-ray films of unusual shadows in and around the sella. In one case, of many years' standing, the trouble was thought to have originated in a chronic sphenoidal sinusitis. This patient, whose principal complaint was continuous sleepiness, is said to have been entirely relieved by oral administration of pituitary gland (character of extract not mentioned, presumably desiccated whole gland).

TUMORS OF THE PITUITARY GLAND.

This division of the subject is mostly of surgical and pathological interest, but many relations to medicine as well are involved.

Cysts.—Cysts of the pituitary gland are not very uncommon. They may arise from rests of the cranio-pharyngeal duct. Echinococcus cysts have been reported. Cysts may result from central softening of a cellular tumor. Cysts of the pars nervosa are thought to arise from snaring off of a part of the infundibular diverticulum from the third ventricle.

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[1] Loc. cit., p. 50. (P. 25 of this book.)

[2] Am. Jour. Med. Sci., April, 1922.

Fibrosis.—Fibrosis may result from healed gumma or from sclerotic changes following cellular hyperplasia.

Cellular Tumors.—Various cellular tumors have been described. Hyperplasias and strumas are relatively small. Their cellular make-up is like that of normal gland. Adenomata of the anterior body, carcinomata and sarcomata, developing gradually, will not infrequently erode or bulge the bony walls of the sella below, before and behind, or cause absorption or distortion of the clinoids; above, they break through the dura mater into the brain. Bony growths in the neighborhood of the sella, or cellular tumors of near and distant regions of the brain may directly or indirectly compress the gland or interfere with its blood supply. In the stalk cysts and cellular tumors also occur. For details the large works on surgical pathology and neoplastic diseases may be consulted. Ewing's account[1] is excellent, and J. P. Simonds'[2] article is of great interest and value.

Symptoms and Signs.—The usual signs and symptoms of brain tumor may be observed—epileptiform convulsions, vomiting and headache. Changes in the retina may occur early—atrophy, choked disk, restricted visual fields, bitemporal hemianopsia. A variety of palsies of the external muscles of the eye have been described. In adults various symptoms of mental aberration and in children retarded mental development, imbecility and actual idiocy have been noted. In addition to the usual signs of pressure and of new growth, there may be clinical evidences of dyspituitarism (see later sections). Upon these most frequently an accurate localization of the lesion will depend. When the floor of the sella has been broken through by a tumor, cerebrospinal or cystic fluid may escape through the sphenoid sinuses into the nose (*rhinorrhea*). Nosebleed is also common.

Diagnosis.—A history of syphilis and a positive Wassermann will be helpful, though even in the proved presence of a general luetic infection the growth may be something else. Roentgen-ray films or photographs are indispensable. This diagnostic resource was apparently first introduced by Oppenheim.[3] All the resources of the roentgenologist should be employed, and profile plates and films, direct and stereoscopic, should be studied. The appearances are various. In acromegaly, irrespective of the character of the growth, the walls and processes of the sella may be much thickened. In case of cysts and cellular tumors the bony tissues may be thinned, eroded, "ausbuchtet" (Oppenheim), partially absorbed or completely destroyed. Roentgen-ray photographs are not always easy to read. In small children, unless an anesthetic is given, the exposure may be defective. In all cases one must remember that there are wide limits to the normal variability of the bony structure of the sella. Probably a vertical of 14 mm. by a horizontal of 15 mm. on the film may be taken as the extreme of adult dimensions of the sella consistent with normal function of the gland. In small women and all children such a measurement is probably pathological. All readings should be conservative, and be carefully correlated with the clinical signs. The roentgen-ray outlines will from the nature of the exposure be always somewhat magnified. As this enlargement affects all photographs to nearly the same degree, comparative figures are reasonably reliable. In the same patient a succession of films at convenient intervals will give some notion of the growth of a suspected tumor, or of its recession. One must be careful to remember that the roentgen-ray gives diagnostic information of the size, shape and growth of a neoplasm, but *not* of its structure. Cysts, of course, tend, as elsewhere, to assume a spherical outline, but inferences should be guarded. Roentgen-ray photographs are mentioned again (p. 186).

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[1] Neoplastic Diseases, 2d ed., Philadelphia, Saunders, 1922.

[2] Barker's System.

[3] Arch. f. Psychiat., 1901, **34**, 303.

Gordon and Bell[1] studied the size of the normal sella in 104 normal children. The profile roentgen-ray film showed a hollow which might be round, oval or "saucer-shaped." The largest measurements, 10 by 8 mm., occurred at four and five years. The smallest was in a girl, aged nine years. "The size and shape of the head have no relation to that of sella."

C. H. Jewett[2] has studied 100 normal fossæ in adults, aged sixteen to eighty-one years. A wide range of shapes and sizes was noted; absence of processes was not pathological; "bridged-over" sellas were 10 per cent of the whole number, and not pathological, but probably due to the superimposition of shadows. The biggest sellas averaged 10.6 by 7.6 mm.; the smallest averaged 9 by 6 mm. "Diagnosis must be correlated with clinical signs." A. Schueller[3] gives an extended and valuable series of diagrams of the sellar profile in adults and children. He also mentions the bridge of bone between anterior and posterior and even middle clinoids as sometimes the "only abnormality."

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[1] Endocrinology, 1923, **7**, 52.
[2] Am. Jour. Roentgenol., 1920, **7**, 352.
[3] Loc. cit., p. 308.

Treatment.—Since Victor Horsley's remarkable work upon brain surgery in 1886 *surgical methods of treatment* have been viewed in a more hopeful light. The technique of the operation for approaching the pituitary region has been closely studied by surgeons, and the advantages and disadvantages of the trans-sphenoidal, intranasal, subtemporal and other routes are fully set forth in the standard text-books of surgery. Cushing[1] summarizes surgical methods as of value for the drainage of cysts, the relief of pressure symptoms and (by partial excision) the reduction of excessive output of the anterior lobe.

If syphilis be proved or suspected the current antisyphilitic medicines are indicated.

Surgical methods may often be usefully supplemented by *roentgen-ray therapy.* Blumberg[2] gives a recent favorable review of this treatment. Cure is hardly to be expected, but relief of headache may be obtained, and enlargement of the previously restricted visual fields. No general directions for duration of exposure, strength of ray and intervals between treatments can be given. Such matters must be decided for each case as it comes up.

DISORDERS OF SECRETION.

In this book disorders of secretion of whatever kind are spoken of as *dyspituitarism,* and more specific terms are employed to denote the precise character of the deviation. This division of endocrinology is one of growing interest and importance. The following paragraph from the Preface of H. Cushing's classic text-book[3] has lost none of its significance:

"There is every reason to believe that the cases of clinically recognizable pituitary disease are at least as common as the cases of clinically recognizable thyroid disease, and despite the wide publicity among the profession of matters relating to dysthyroidism, it is unquestionable that in only a small proportion of the individuals affected with low-grade functional diseases of the thyroid is the nature of the malady appreciated. How much more this is true of pituitary body disorders needs no comment."

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[1] Loc. cit., p. 161.

[2] München. med. Wchnschr., 1922, **69**, 739.

[3] Loc. cit.

Dyspituitarism may be due in theory, as in case of other endocrine glands, to *excess, reduction, absence* or *toxic alteration* of secretion.

In respect of *toxic alteration* of pituitary secretion, little or nothing is known. Neither the physiological facts nor the clinical conquences are more than hypothetical. For the time (1) the argument from analogy that the thyroid probably has toxic deviations, and (2) the clinical signs of "toxemia" in certain cases of acknowledged pituitary disorders (differentiating them from the more common pituitary troubles, such as anomalies in the growth of the bones, changes in metabolism, polyuria, glycosuria), may be allowed as reasons contributing to the probability of such a view. At present no more exact statement can be made. "Toxic pituitarism" is apparently capable of appearing in connection with, as a precursor, or as a sequel of any of the simple forms of hyper- and hypopituitarism. The present-day writers seem in a general way disposed to explain most mental concomitants of pituitary disease (not readily explicable as due to pressure) as "toxic" effects. This is only a pleasing clinical assumption, and at that not a unanimous one. Professor Marie, writing to Professor Cushing,[1] in 1911, expressed the belief that even acromegalia may be a toxic pituitarism. Simmonds' disease suggests a toxic pituitarism.

With this confession of weakness, one may proceed to say that the facts in connection with the other possible abnormalities of the pituitary gland, while they are fragmentary and imperfectly correlated, are on a much firmer experimental basis. What is known to-day, or what may be rationally inferred from laboratory and autopsy work and bed-side studies, is set forth in the following sections with every attempt at avoidance of exaggeration and of speculative presumption.

A final note is necessary, namely that while in actual clinical experience clean-cut affections of a single lobe, either in the direction of plus or of minus secretion, are not generally met with, I have for purposes of clearness sketched first and at some length the relatively simple "plus" and "minus" disorders of each part of the pituitary, and have collected in later paragraphs the additions, exceptions and explanations that are required in order to cover the clinical appearances in mixed disorders.

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[1] Loc. cit., p. 249, note.

SECRETORY DISORDERS OF THE ANTERIOR LOBE.

HYPERPITUITARISM OF THE ANTERIOR LOBE.

This condition has one typical clinical type in the strange disease *acromegalia* or *acromegaly* (enlargement of the extremities). The original account of P. Marie, in 1886, already alluded to, contained full notes, with illustrations, on 2 cases of his own, with several more from the literature. The New Sydenham Society translated his paper and published it in 1891 with additions, giving very fully the main characters of the disease. Marie himself then supposed it due to pituitary deficiency. Cushing,[1] as I have just noted, quotes Marie in 1911 as inclining to the view that acromegaly may be a toxic pituitarism. Subsequent writers have, on the contrary, concluded quite generally that hyperpituitarism is present. This is the general view to-day. J. Parisot[2] has urged that it is of pluriglandular origin. For Bailey's view see p. 165.

Etiology.—Excessive secretion is generally due to a cellular tumor; the etiology is generally the etiology of tumors, ultimate cause of origin unknown. In some cases in which, as in self-limited cases of Graves's disease, the gland first takes on the histological appearances of adenoma, but after months or years begins again to involve, one may suppose that the defensive mechanisms of the animal economy have automatically gotten to work, but precisely how this happens is quite unknown. Various enthusiastic speculators inform us that the process is one of antagonistic action by other endocrine organs; but this is pure supposition, entirely unsupported by any consensus of experimental or clinical facts. Cellular tumors elsewhere from time to time give evidence of regression and of variations in growth energy. The question must be left to the future for decision.

Pathological Anatomy. The pathological anatomy in fatal cases brought to autopsy has been closely studied. As regards the pituitary gland itself, the appearances have been very various. The typical condition is hyperplasia or adenoma of the anterior lobe. Hyperplasias and strumas once active may have subsided or become fibrous when the case comes to autopsy. This may account for the occasional reports of a normal gland. Many tumors of the pituitary gland (of various histological appearances) run their entire course without signs of dyspituitarism. It is obvious that many such, as in the comparable case of the thyroid, are of a structure which does not promote secretory activity, or even retards it. Schuster[1] reported, out of 775 cases of cerebral tumor with psychosis, 60 tumors of the hypophysis. Only 12 of these were associated with acromegaly; 7 patients out of the 12 were weak-minded; 5 were actively insane.

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[1] Loc. cit.

[2] Rev. neurol., 1910, **19**, 277.

It must be noted, therefore, that acromegaly is found *with* and *without* pituitary tumors, and that pituitary tumors are also found without acromegaly. Possibly the contention of B. Fischer,[2] that if acromegaly be present hyperplasia or tumor is always present, *i. e.*, that none of the reports of "normal" glands is free from objection ("einwandsfrei"), is too radical, but J. Ewing[3] thinks it "not far from a demonstration." Admitting that some are microscopically "normal," chemical or circulatory changes may still excite a hypersecretion.

Pressure alterations made by pituitary tumors in the skull have been mentioned (p. 176). *Pathological changes of secretory origin* in the skeleton, sex organs and skin are characteristic. To avoid repetition the reader is referred to the next paragraph (Symptoms), under which they are more conveniently described

Symptoms.—There is no distinction of sex in the incidence of the disease, and it occurs both in adults and children. The commonest period of onset is between the twentieth and thirtieth year. The symptoms and signs in these typical cases will be first described, with subsequent notation of the differences observable in children.

The hands and feet are much increased in size. The enlargement is due both to increase in size of the bones and thickening of the soft tissues. Bony exostoses may appear. Genu valgum is common. The joints are, however, not crippled; fine adjustments can still be made. A woman so affected can still thread a needle if not blinded by the tumor. Skilled artisans often continue at their trade. The finger-nails and toe-nails are very much broadened. The head increases in volume; the face in length and breadth. The sutures have been sometimes found (at autopsy) obliterated. The upper and lower jaws may grow so that spaces are left between the teeth, such as appear between the milk teeth of growing children of four and five years of age. Sometimes the ears grow to an immense size. The thorax and vertebral column are involved later on, and the back becomes markedly humped (kyphosis). The skin is rough, thickened and folded. Sweat and oil glands are still active. Pigmentation of the skin has been noted, but this may be due to adrenal or various other accidental complications. There may be hypo- or hypertrichosis. Cushing[1] reported a man with excessive growth of hair over trunk and arms. Muscular asthenia is sometimes marked. The larynx is much enlarged, and the voice becomes deep-toned and harsh—a condition possibly due to larger resonating sinuses as well as a larger larynx.

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[1] Psychische Störungen bei Hirntumoren, Stuttgart, Enke, 1902, p. 205.

[2] Frankf. Ztschr. f. Path., 1912, **11**, 130.

[3] Loc. cit.

The *sex functions* may be excited early in the disease. Later on menstruation is suppressed, as a rule, and impotence may occur. Cases beginning before puberty may be accompanied by sexual infantilism, with small uterus or testes and deficient pubic hair. This is not by any means an invariable rule.

Changes in the blood and blood-pressure are not characteristic. Hyperglycemia presumably precedes the glycosuria mentioned in the next paragraph. Exact notes in the literature on this point are hard to find.

Urinary Changes.—Albuminuria and inflammatory conditions in the urinary tract are secondary. Glycosuria is frequently encountered in the early stages of the disease. It is attributed commonly to a presumably coincident stimulation of the posterior lobe. It may be due also to diabetes of pancreatic origin, or to errors of diet, or to other causes (p. 264). In later stages it disappears, and the carbohydrate tolerance may be even increased. But various patients differ extremely.

The *basal metabolism* in acromegaly is mentioned on page 173.

Central Nervous System.—*Psychoses.*—Manic-depressive states, paranoia, dementia and mild conditions of mental apathy and weakness are described. P. Bassoe[2] associates pituitary psychoses with the mental disturbances of the climacteric, and derives them from the "precocious sexual involution" commonly coming on in the late stages of the disease. It seems to me more rational to consider these conditions as due to the tumor or to cerebral troubles of independent origin rather than to the dyspituitarism. The data are insufficient for a conclusion. Some historical giants have been terrible liars and drunkards.

Pressure symptoms caused by the enlarged pituitary gland are variable. They depend on the speed and direction of the growth. Headache is often severe and tormenting, and may be variously located. Cushing notes the exceptional frequency of bitemporal headache. Sleepiness (p. 207) is quite characteristic; it passes in later stages into stupor. Any or all the signs of cerebral tumor may present themselves, together with those especially connected with tumors at the base of the skull, such as primary optic atrophy, bitemporal hemianopsia and various palsies of the external ocular muscles.

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[1] Loc. cit., Case 25.

[2] Barker's System.

Gigantism.—In children (more often boys) who have not completed their growth (girls under seventeen, boys under twenty or twenty-one years) the presence in the general circulation of excessive secretion from the anterior lobe (as is supposed) seems to delay synostosis of the epiphyses and diaphyses of the long bones, and growth is irregularly continued for an indefinite period (up to fifty years in one case), with the production of *gigantism.* Osler stated years ago that "The skulls of some notable giants show enormous enlargement of the sella Turcica." The height of 8 or 9 feet may be sometimes reached. Familial gigantism is sometimes observed. If growth stops acromegalic deformities may be superadded. Gigantism has a large literature. Studies by C. L. Dana[1] and W. Hutchinson[2] are valuable. The volume by Launois and Roy[3] is encyclopedic. (See Chapters XIV and XV for other details.)

There is a general impression to be gathered from classic English literature that physical giants are apt to be mentally deficient. The old jest attributed to Sir Francis Bacon, that "A very tall man is apt to be like a dwelling house—the attic lacks furniture," illustrates the same idea. Charlotte Brontë's delightful paragraph in *Shirley* (Chapter I) is in point:

"See what a big, vacant Saph he looks at this moment!"

"Saph! Who was Saph, Sir?"

"I thought you would not know! You may find it out: it is biblical [II Sam., 21, 18]. I know nothing more of him than his name and race; but from a boy upward, I have always attached a personality to Saph. Depend on it he was honest, heavy and luckless; he met his end at Gob, by the hand of Sibbechai."

Walter Scott (*Kenilworth,* Chapter 26) writes:

"The gigantic porter who waited at the gate beneath, and actually discharged the duties of warder, owed none of his terrors to fictitious means. . . . The head of this formidable person was uncovered except by his shaggy black hair, which descended on either side around features of that huge, lumpish and heavy cast, which are often annexed to men of very uncommon size, and, which, notwithstanding some very distinguished exceptions, have created a general prejudice against giants, as being a dull and sullen kind of person."

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[1] Jour. Nerv. and Ment. Dis., November, 1893.

[2] New York Med. Jour., 1898, **67**, 341; and 1900, **72**, pp. 89, 133.

[3] Études biologiques sur les géants, Paris, 1904.

There is, however, a wide range of physiological variation both in length of body and strength of brain. Some very tall men are gifted not only with talent but with the far rarer quality of personal charm. It is impossible to say where a pathological hyperpituitarism in growing boys and girls begins and normal growth ends.

Diagnosis.—The diagnosis is to be based upon the history, the age of the patient, the roentgen-ray photographs and the symptom-complex. Osteitis deformans is sometimes suggestive of acromegaly. Hypertrophic pulmonary osteoarthropathy, and certain cases of syringomyelia have been mentioned in the literature as presenting unusual resemblances. Leontiasis ossea, mentioned in Marie's first paper, is so rare as to cause but little difficulty. One should not allow himself to be hurried too soon into a definite diagnosis; most of the problem cases can be solved after a reasonable amount of study. Myxedema also was mentioned in Marie's original account as an additional source of confusion.

Course and Prognosis.—These vary with the causation of the disease. Malignant growths generally progress with more or less speed to a fatal termination. Some cases advance rather steadily for some months or years and then become stationary, or even lapse after a time into a state of hypopituitarism. This event is comparable with the hypothyroidism or mild myxedema occasionally following a prolonged attack of Graves's disease. In benign or recessive cases the mind may be entirely unaffected. Men of large business or professional responsibilities sometimes successfully keep at their work for years.

Treatment.—In rapidly progressive and alarming cases of what seems to be a malignant pituitary growth, operation, if it is to be done at all, should not be delayed. J. W. Hunter, Jr.[1] makes a very discouraging report on 5 recent cases of pituitary adenoma. Cushing's results have been more promising. Benign cysts offer a better operative prognosis than cellular tumors. Therapeutic roentgen-ray exposures have been already mentioned as a source not of cure but of relief.

In the earliest stages of the pituitary struma one might, from thyroid analogy, rationally hope to ease off the strain on the gland by giving extract of anterior lobe. It is, of course, contraindicated during the active progress of the disease.

Expectant treatment is sometimes advisable in view of the fact that the cases are occasionally self-limited. When a hypopituitarism finally supervenes anterior lobe extract or whole gland may be given. The general condition and the feelings of the patient at this stage are said to be often much improved by gland therapy; the skeletal deformities are permanent. With this condition we may again compare the permanently enlarged thyroid, the prominent eyes and the irreparably damaged heart in some "cured" cases of Graves's disease, which have gone over into a hypothyroid state.

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[1] Va. Med. Monthly, January, 1922.

The physiology and therapeutics of gigantism are ill understood. Administration of a physiological antagonist of anterior pituitary would theoretically stop a tall boy or girl from growing beyond the normal, but the endocrine antagonisms are as yet a closed book in this regard. After synostosis has occurred and overgrowth has been organically completed there is no rational resource.

HYPERPITUITARISM OF THE POSTERIOR LOBE.

Hyperpituitarism of the posterior lobe, so far as I am aware, has never been identified as an uncomplicated clinical entity. In theory the symptoms would be (see Physiology, p. 160) increased metabolic activity, loss of weight, diminished capacity for carbohydrates, intermittent glycosuria, raised blood-pressure and possibly supernormal temperature. Some of these signs accompany hyperthyroidism, but they are not diagnostic of any known disease. With an irritative lesion of the posterior pituitary they might be sometimes found as precursors of the Froelich syndrome, but that the Froelich cases are not seen in time. It may be that some cases of glycosuria, following fractures of the base of the skull, blows on the head and various lesions of the soft tissues of the base of the brain, are due to irritation of the posterior lobe. These are at present matters of speculation only (p. 172).

HYPOPITUITARISM OF THE ANTERIOR LOBE.

Causes.—Tumors and cysts of the gland or luetic deposits can quite readily destroy or injure the cellular parenchyma by direct pressure or by occlusion of the nutrient vessels. Tumors of the neighborhood may compress the gland, especially tumors of the stalk, which are by no means uncommon in the whole mass of brain tumors in general. Degenerative or inflammatory changes accompanying a recessive hypertrophy or hyperplasia may produce the same result.

There seems reason to conclude, in view of the purely chemical changes that we seem compelled to assume in the islets of Langerhans in some cases of diabetes, that in the pituitary gland also depressing chemical and circulatory changes may occur which are not accessible to microscopical discovery. These for the present we must call "functional." They have at least one definite character—they are amenable to medical treatment.

Symptoms.—Roentgen-ray photographs in children and young adults suspected of anterior lobe deficiency are often negative. They sometimes show, as also happens, and perhaps more frequently, in posterior lobe deficiency, a "hooded" sella, that is, one in which the anterior and posterior clinoids overlap one another, or a shallow sella. This happens often enough to justify the suspicion that such an arrangement interferes with the circulation and growth of one or the other or of both parts of the gland. It is not, however, in itself a pathognomonic sign of pituitary dysfunction. It is of value only in its relations to the symptom-complex. It is also sometimes seen in people without clinical signs of any disease.

Subacute symptoms slowly developing in adults are obscure. When the patient is long convalescent from acromegalia, but still complaining of "not feeling well," hypopituitarism of the anterior lobe may be suspected. After operation on the anterior lobe, with destruction or removal of too much tissue, the symptoms are described by Cushing as fulminating; collapse comes on quickly and death may ensue in a few hours or days. In the light of newer knowledge, this may or may not be due to acute apituitarism. In adults where there has been nothing previously to indicate anterior pituitary trouble, or invite attention thither, I doubt if the diagnosis can be made. Simmonds' disease *might* belong here; its precise chemical pathology is obscure.

In children and in young people (of either sex) under twenty years of age the most characteristic sign of anterior hypopituitarism is retarded physical growth, *physical infantilism.* This must be differentiated from the stunted growth of cretinism (Brissaud's type of infantilism), of malnutrition, of achondroplasia and of chronic cardiac disease. C. A. Herter[1] also described cases of infantilism due to intestinal infection. Byrom Bramwell[2] reported a case of "pancreatic infantilism." The malnutrition cases are often but not always found in city tenements. Malnutrition and neurasthenia among adolescent children of the well-to-do, due to overexcitement, overfatigue and loss of sleep, are accompanied by a poor and capricious appetite and a complete arrest of growth. The cardiac cases are also in a class by themselves; the retardation of growth is secondary. The hypothyroid children are discussed elsewhere. They are sufficiently marked in most instances by the specific stigmata. The achondroplastic dwarf (p. 352) makes an entirely different clinical picture. There is an elaborate study of infantilism by G. Peritz,[1] from which additional details may be gathered.

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[1] Infantilism from Chronic Intestinal Infection, New York, Macmillan, 1908.

[2] Scottish Med. and Surg. Jour., 1904, **14**, 321.

The *Lorain type* (Lorain, 1871) *of infantilism* is thought by French writers to be a special form. The stature is only moderately reduced; the patient looks like a small man or woman, but is weak and thin. The mentality is childish. The precise lesion of the pituitary (if there be one at all) in these cases is doubtful. Brissaud[2] ascribed to anangioplasia the origin and symptoms of the disease.

Children *properly classified* as physical infants are not especially dull; they are often mentally bright, well up with their classes, of amiable personality and often of considerable charm; but they fail to grow. The parents usually date the arrest of growth from some intercurrent shock, injury or illness, but this is obscure. Roentgen-ray films may or may not show a "hood" or a small and shallow sella. Many of these cases seem to have a "functional" deficiency of the anterior gland, such as has been described above, with the sellar pictures negative.

When such children are "crying every five minutes," bad-tempered, dull, noisy, immoral, vain, sly, mendacious, disobedient, destructive, pugnacious, and untidy, *as well as* undersized, I am accustomed to doubt the diagnosis of simple hypopituitarism and to look for organic changes in the brain or general toxic conditions to which hypopituitarism is perhaps superadded only as a secondary condition. This question is considered also on p. 179.

Prognosis.—The prognosis in each case must be an individual one, depending on the cause. When the cause is a malignant tumor the prognosis is virtually hopeless. Cysts offer a better surgical prognosis. Antispecific treatment will benefit the luetic cases, and opotherapy some of those which have reached a terminal hypopituitary condition after a long attack of acromegaly. Opotherapy is quite promising in the simple infantilism of boys and girls. It will often do some good in the secondary conditions above described, but a cure cannot be hoped for from pituitary alone.

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[1] Ergebn. d. inn. Med. u. Kinderh., 1911, **7**, 405.

[2] Rev. neurol., 1900, **8**, 523.

Treatment of Anterior Lobe Deficiency.—It has just been mentioned that opotherapy (see section on Pituitary Therapeutics) may be of value in the terminal stages of acromegaly. Operation is the only treatment for progressive tumors and for cysts. When at operation too much gland has been accidentally or necessarily removed, the "acute surgical apituitarism," which Cushing found an alarming and rapidly fatal accident (on this point see p. 165), may possibly be controlled by large oral doses of gland extract or (a counsel of desperation) by transplanting a gland. Cushing[1] thinks he did this successfully in one case. The transplant was taken from the skull of a new-born infant dying of hemorrhage, and was planted in the cortex cerebri. (The general theory of gland transplantation is set out in Chapter XIV.)

Of the treatment of simple infantilism in boys and girls I have already written with some hopefulness,[2] as follows:

"Primary anterior lobe deficiencies of a 'functional,' or at least of a temporary and curable character, may be suspected in boys and girls of the 'infantile' type, in whom a complete examination carefully and repeatedly made is negative for any organic lesion in the brain and sella, and in whom the mentality is not deficient nor the thyroid gland at fault. A long series of New York Public School children of this character have passed through my hands at the Good Samaritan Dispensary in the last fifteen years. They receive whole pituitary (special formula prepared for me by a New York wholesaler) in suitable doses, and in the course of one or two years they grow remarkably, to the delight and admiration of themselves and all their family connection. One small boy, aged fourteen years, stationary for four years previously, grew nearly 10 inches in the year after treatment was begun, and developed all the external signs of puberty. He was a bright and attractive boy otherwise, a monitor at school and a favorite with teachers and comrades. He was a half head shorter than a normal younger brother of twelve years when the treatment was begun.

"Such diagnoses are confessedly only clinical guesses. The old fallacy, *post hoc, ergo propter hoc*, is not excluded; but frequent repetitions of such an experience increase one's confidence that a correct diagnosis has been made. The 'lame' anterior gland, after use of the therapeutic 'crutch' for a few months or years, is able to walk alone again. The same thing happens in minor grades of hypothyroidism after giving thyroid.

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[1] Loc. cit.

[2] Forchheimer-Blumer System of Therapeusis, New York, Appleton, 1925.

"One remarkable case of a boy, aged seventeen years, who had made good progress through the grades but was falling behind at high school, illustrates the negative side of the last paragraph. He was very small, and had not grown any since his tenth year. He was also pale and thin, and had a piping voice and a curious senile look, accentuated by small wrinkles at the outer angles of the eyes. The mentality was good. He wore glasses, but the eye backgrounds were reported normal by a very competent oculist. The physical examination and the urine were negative. He had no headache and no history of fits. Pituitary failed to do him any good, and he one day very unexpectedly had a fit, and two days later another; in the latter he died. The autopsy showed a moderate-sized cellular tumor of the pituitary stalk. This case might be symptomatically compared in some ways with the curious *progeria* of Hastings Gilford (p. 354), though it has also relations with the Lorain type of infantilism."

The therapeutic results above mentioned will not occur unless a properly made extract is used. Although only the anterior gland is apparently at fault, I have followed Cushing's suggestion and given whole gland in the belief that the posterior gland is very likely a participant to a certain extent in the local disturbance. An experience of E. B. McCready[1] indicates how much time may be wasted with inert extracts. The "whole gland" he mentions in the following paragraph was made after my formula.

Dr. McCready's patient was diagnosed as a case of infantilism with hypophyseal insufficiency. He was nearly sixteen years of age when first seen; height, 4 feet 3½ inches; weight, 59 pounds. There was a history of poverty and neglect, and the boy had chewed tobacco, run upon the street, eaten irregularly, been sometimes drunk, and never required to go to school. Sella small, with shadows suggesting a tumor. Epiphyseal ossification delayed. Urine excessive in amount, colorless, of low specific gravity.

"For the first three months he received a tablet containing very small doses of thyroid, thymus, pituitary, testicular and suprarenal extract. For the last of the three months he received in addition 2 gr. extract anterior pituitary. During this period absolutely no gain in height resulted.

"He was then placed upon 1 capsule daily of desiccated whole fresh ox gland mixed with milk sugar to standard dosage. In three weeks he had gained $\frac{3}{4}$ inch, and to the present date (about ten weeks) has gained $1\frac{1}{2}$ inches. He has gained markedly in coördination, in gait and in activity. When first under observation the slightest exertion tired him so that he was compelled to sleep or rest. He is now able to take a walk of several miles without undue fatigue. The change in the boy's appearance is so great that his father states he should hardly recognize him as the same boy."

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[1] Illinois Med. Jour., October, 1914.

When anterior hypopituitarism is accompanied by and is (as I believe) secondary to the graver defects of adolescent manners and morals that I have just alluded to opotherapy may produce a relative improvement. "Cure" is not to be thought of unless the primary cause of the trouble can be located.

HYPOPITUITARISM AFFECTING CERTAIN FUNCTIONS OF BOTH LOBES OR OF THE POSTERIOR LOBE ONLY.

Two diseases may be provisionally classified here, *Froelich's disease* and *diabetes insipidus*. The latter is associated at times with a frank dyspituitarism, and at times appears alone. It is discussed in the following section.

Froelich's Disease (*Cerebral Adiposity, Dystrophia Adiposogenitalis*).—This is generally attributed to a partial hyposecretion of both lobes of the pituitary. Though it appears also to result from experimental lesions of the tuber cinereum, it has not yet been proved that such lesions do not interfere with the circulation in the intrasellar gland.

Causes.—Lues seems to be at the root of some of the cases. A few cases of Froelich's syndrome following lethargic encephalitis have been reported. For references the recent paper of Symonds and Eckhoff[1] may be consulted.

Malformations of the sella—the "hood" with overlapping processes, a shallow sella, a very small sella—may be shown by roentgen-ray, and will suggest compression or vascular strangulation. This question has been fully dealt with elsewhere (p. 186). It must, however, always be remembered that especially in children the bones are soft, and compression may be more apparent than real.

Tumors of the pituitary have already been discussed. Pressure may also be produced by transfer from neighborhood tumors. Some tumors of the pineal gland have been associated with "cerebral adiposity" (p. 309). Tumors of the stalk have been frequently found at autopsy. But they may also exist with good function of the posterior lobe, the pressure being apparently exercised in other directions. Pituitary cysts are not uncommon. A recent patient of mine, a young woman, 5 feet 2 inches in height, showed in the profile roentgen-ray films a rounded shadow fully 16 by 16 mm. in dimensions. Destructive tumors of the sella, as shown by roentgen-ray, sometimes do and sometimes do not produce signs of pituitary deficiency.

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[1] Guy's Hosp. Repts., 1924, **74**, 402.

When roentgen-ray films are negative, analogy still at times justifies the opinion that in many of the chronic cases there is trouble of a functional character.

Frequency.—The Froelich syndrome is by no means a rare disease. It occurs both in males and females. Many of the cases go for years without either diagnosis or treatment. As with gigantism there is possibly a familial tendency to the disease, if one may judge from the rather frequent appearance of two or three cases in one family. It may be, however, that as in cases of supposed inherited deafness, all that is passed down is a bony contour favorable to the development of the condition.

Symptoms.—The classic symptoms of pituitary deficiency may be inferred from the notes on the physiology of the gland. It has been already noted that Froelich, in 1901 (p. 162), first identified as a clinical entity the concurrence in one patient of increased carbohydrate tolerance with adiposity and more or less complete involution of the sex organs. The weight of the patient may be remarkable. A lady recently in my care for this trouble was 5 feet 1½ inches high and weighed 207 pounds. In men impotence, in women amenorrhea, is apt to develop prematurely. In children the sex organs retain their infantile appearance. Lisser[1] found the prostate rudimentary in boys. Where the pars anterior is not much damaged, growth of the bones and development of the gonads in children may, however, continue as usual, with a greatly disproportionate accumulation of fat, particularly around the belly or over the hips. The patient may even be unable to lace his own shoes or remove his stockings. Some subjects of this disease make their living as objects of interest in "side-shows," along with the midgets and the bearded ladies. The temperature and blood-pressure are not greatly altered in either direction; they are, however, more apt to be lowered. The patient can often take much more than the normal 100 gm. of glucose without glycosuria.

Local symptoms and signs (choked disk, blindness, headache, vomiting) will depend on the nature of the causation. They are often absent, and the condition of the pituitary is negative as far as the patient's feelings go. Many of the patients are perfectly comfortable, mentally acute, well capable of taking care of themselves in the world and very unhappy when their supply of food is reduced. I have known intimately some sufferers from this disease, and have found them good conversationists, wide readers and of excellent business talent. One little girl recently sent me from a Southern State led her class at school, was of a happy and pleasant disposition, obedient, patient with small brothers and sisters, and tidy. She was of a good height (53 inches) for her age (eight years), but weighed about twice too much (102½ pounds). Her sella was small, and only 4 mm. deep.

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[1] Endocrinology, January, 1922.

The following case is of special interest,[1] in view of the possibility that an irritation of the posterior lobe with posterior hyperpituitarism (glycosuria) preceded the later development of a mild Froelich syndrome.

F. S., a female, now aged eighteen years, single, living in Brooklyn, American-born, of Jewish parents, stenographer, first came to my Clinic nine years ago. Her mother brought her for some intercurrent medical complaint which required no special treatment, and she was well in two or three days. Family history negative, except as noted below. Stature normal.

Noting that she "blinked" continually, we referred her to Dr. C. B. Broder, of our Eye Department. Dr. Broder made the diagnosis of interstitial keratitis, and for this she was treated for some time, improving slowly. Her Wassermann was negative.

Two years later her mother brought her to me again. She had grown, and was a good-sized girl for eleven years, well grown, nothing more. She now had certain symptoms of renal disease. Her urine was examined at once, and showed abundant albumin, red blood cells and epithelial casts, also a marked positive reaction for glucose. We could never get a good twenty-four hours' specimen, but casual samples tested as high as 2 per cent sugar. Inquiry showed that her mother and two of her mother's sisters had or had had diabetes. (One of the latter has since died at about forty-two years of age, of diabetic gangrene.)

Neither the patient nor her mother could be convinced of the gravity of the girl's condition. Ambulatory treatment failed entirely from lack of coöperation. I therefore presently referred the girl to Mt. Sinai Hospital. Here she stayed some weeks, but later returned, still running albumin and glucose as before. Yet all this time her general condition seemed good; her blood-pressure was low and her physical examination negative.

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[1] Berkeley, W. N.: Med. Record, October 8, 1921.

She now disappeared again from observation, and two years later reappeared, thirteen years of age. She said she had had no treatment, and had eaten what she wanted. Her urine was now normal as far as we could determine; there was no albumin, no glucose. She had grown and fattened, had a bright color (her own!), well-developed breasts and all external signs of puberty, though she was said not yet to have menstruated.

Three years later she again came about some intercurrent trouble. She appeared to be in perfect health; no albumin, no sugar. Blood glucose carefully determined at this time showed 0.11 per cent (two hours after breakfast). She asked for a letter that she might be admitted to the list of "farmerettes" for that summer (the World War was in full blast). She said she still had not menstruated.

After dropping from sight for two years more her mother brought her in January of this year (1921), desiring treatment for the persistent amenorrhea. At this time her weight was 149 pounds (clothes on); her height, 5 feet 3 inches in stockings. Her blood-pressure was 112 systolic (mercury manometer); color a little pale; intelligence fully normal. She had no headache; her visual fields were reported from the Eye Department to be unrestricted; her urine was entirely negative. She was working every day.

Dr. J. M. Steiner, of New York, kindly described for me the condition of the sella in profile roentgen-ray films made at this time as follows:

"*Sella Turcica.*—Both the antero-posterior and perpendicular diameters of the sella are materially reduced in size. This is due very largely to the excessive length and width of both the anterior and posterior clinoid processes. The latter incline sharply forward and I believe are adherent to the anterior clinoids. The floor of the sella is smooth and rounded and without evidence of erosion or destruction."

The condition suggested simple hypopituitarism as a provisional diagnosis, and therapeutically I did not think the case hopeless. I prescribed thyroid gland, to be followed a few weeks later by thyroid and whole pituitary combined, as soon as I should have determined the tolerance of the patient for thyroid alone. Again, however, she failed to come back. When we last heard of her she had stopped her medicine; she "should lose her job if she came during business hours," she reported. Her condition was said to be unchanged.

Many of the long-standing cases complain bitterly of muscular and fascial pains, like those of adiposis dolorosa (p. 354).

The *basal metabolism* has been studied with care in some of the Froelich cases. One patient of my own had a basal metabolism of −17. She said that −15 and −21 had been found at two well-known hospitals where she had previously sought advice. Some valuable data on this subject have been already summarized p. 173).

Diagnosis.—All the signs must be rationally correlated. The extreme adiposity is the symptom that usually brings the patient for medical advice. This condition is not always easy to explain. Extreme corpulence is also due (p. 354) to overeating, lack of exercise, excessive beer-drinking, hypothyroidism and various ovarian deficiencies. Of adiposis dolorosa no one knows exactly what the etiology is. In older women the history of a premature climacteric, or in younger ones sudden cessation of the menses does not exclude the chance that the adiposity may be of ovarian origin (p. 355). Roentgen-ray films of the sella may help, but the difficulties and limitations in their interpretation are manifold.

When prepuberal onset of the disease can be established, with the presence of a deformed sella and infantile sex organs, the diagnosis is easier, but in milder cases in children the sex changes of puberty may come on at the usual time or be only slightly delayed. The diagnostic problem may therefore be of some difficulty. Except, however, in the evidently pluriglandular cases (p. 343), a clinical conclusion can generally be arrived at.

Prognosis.—The prognosis depends on the facts of each case. It may be of the utmost gravity if a tumor is the cause. If, on the contrary, some stationary benign circulatory or compressive condition is evident, the patient may live indefinitely with only the handicap that the statistics of insurance companies attach to had the disease thirty-five years, and is in an excellent general condition today. The prognosis in young people as regards the begetting and bearing of children is, of course, dubious. In the milder cases treatment with pituitary gland may accomplish overweight. A patient recently referred to me from the West had something. Even without treatment marriage is sometimes fruitful, and the same condition may reappear in the next generation (familial type).

Treatment.—The difficulties and doubts attendant upon treatment with posterior lobe are described in the section on Therapeutics. The posterior lobe extract of commerce is not quantitatively absorbed from the stomach and bowel, if it be absorbed at all. It must be given by hypodermic. I have already noted the lack of proof that this extract represents the entire posterior gland. It is temporarily efficient in its relief of diabetes insipidus. It is doubtful whether it has any effect on the metabolic symptoms of Froelich's disease. Even after prolonged hypodermic use of it in diabetes insipidus there are no reports that it reduces weight or (in therapeutic doses) causes glycosuria, though it may produce asthenia and pallor. Possibly more information is needed as to what a "therapeutic dose" should be.

In the treatment of Froelich's disease the prolonged administration by the mouth of *a whole gland preparation of entire pituitary* is the most rational procedure. It is my impression that encouraging clinical results are to be obtained in this way. Many cases of improvement on such treatment are to be found recorded. The conditions are unfavorable, however, for a definite conclusion. The patient has been comfortable usually for a long time without treatment; he has become habituated to overeating and grows tired of a strict regimen. Among boys and girls in the tenements it is almost impossible to have the daily ration weighed and balanced, and conclusions cannot be drawn when the line of treatment is half-heartedly and irregularly pursued. Reports in the literature are often based upon the use of an inert pituitary preparation, are deficient in many vital details of weighed food and other medicines given and are to be taken with reserve. Further observations based upon a careful and rigid management of the cases are needed.

When the basal metabolism is more than −10 per cent, thyroid may be given to the limit of tolerance, not on the unsupported supposition that thyroid and pituitary are vicariously interactive, for no one knows whether they are or not; but on rational symptomatic grounds in order to speed up fat catabolism. In addition to this the daily ration must be balanced in the usual ratio of 1 part by weight of protein, 1 of fat and 4 of carbohydrate, and the total calories must be gradually reduced (in like proportion) until about two-thirds of the normal allowance for the age, sex, weight and activity of the subject have been reached. This regimen is irksome, but if long enough continued fairly satisfactory results may be expected.

The patient should be weighed at regular intervals, and no attempt made to reduce the weight at a greater rate than 1 and 2 per cent per month; that is, a patient weighing 200 pounds, for example, ought to lose between 2 and 4 pounds per month. Attention should be strictly given to the bowels, by diet and medication, and the daily quantity of water and salts must also be supervised. Many patients seem rather proud of the little water they drink every day. For cosmetic purposes in the case of very stout women massage may be advised to reduce the disfiguring laxity of the hanging folds of skin about the face and neck when the fat begins to disappear in quantity.

Sometimes female patients do not greatly reduce their total weight by this treatment, but the disfiguring masses of fat abnormally and sometimes asymmetrically piled on the belly and buttocks, and around the waist, slowly melt away.

Diabetes Insipidus.—(*Idiopathic Polyuria.*)—This is a disease marked by a chronic profuse diuresis, with thirst. The urine is light and pale, but has no other known deviations from normal.

As a distinct clinical entity diabetes insipidus has been known and written about by medical authors for centuries past. The clinical accounts in the text-books of forty years ago are excellent.

Etiology.—The disease is rare. It is more frequent in males than in females (Osler). It is said to be relatively more common in young people. It has been noted in very young infants, and some authors have collected statistics to show that it is a hereditary trait in some families.

Before considering the etiology further one should note certain symptomatically similar conditions which are quite evidently of a different nature. Osler states that polyuria occurring occasionally with lesions of the abdominal organs (abdominal aneurysm, tuberculous peritonitis) is not a true diabetes insipidus. The polyuria of some people who habituate themselves to drinking large amounts of water, or of workers in German breweries who drink many quarts of beer daily, is the normal consequence of the ingestion of excessive fluid. Hysterical polyuria is also an entirely different condition; it is intermittent, and is associated with other signs of hysteria. Some students of the subject have thought[1] that *polydipsia*, a pathological thirst, is sometimes the primary element in the condition, and that the polyuria is secondary. This hypothesis, Buttersack thinks, may be demonstrated in some cases by the expedient of accurately measuring the intake and outgo of fluid for a given time. Inasmuch as in primary polydipsia there is presumably no disorder of the sweat mechanism, and allowing that loss of water by lungs and stool will be nearly the same in both polydipsia and polyuria, it will be found in primary polydipsia that the urinary outflow invariably falls short of the quantity of fluid drunk, whereas in primary polyuria the reverse is the case, water continuing to escape from the blood by the kidneys and being replaced by withdrawal of water from the tissues, even when the patient refrains entirely from drinking.

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[1] Buttersack, Paul: Inaugural Dissertation, Berlin, Schumacher, 1886.

Every one knows, furthermore, that in chronic interstitial nephritis, after the blood-pressure has risen, large amounts of urine are passed, generally very light and often without albumin or casts. These cases also must be excluded.

The familiar fact that terror, anxiety and excitement often cause a profuse diuresis of light and pale urine needs only to be mentioned. This is a sympathetic reaction, entirely different from the diuresis now in question.

The remaining cases are for various reasons thought to be due to a lesion of the posterior pituitary or its stalk. This is suggested by the results of experimental extirpation in animals, the main data of which have been set forth on a previous page. If the observations of Bailey and Bremer[1] are true, that lesions of the tuber cinereum and not of the posterior pituitary are the cause of the polyuria, one is not thereby driven from the clinical assumption of trouble in *the vicinity of* the pituitary, for the tuber cinereum is directly attached to the infundibulum. In the second place there can be no longer any question that the commercial posterior lobe extracts when given by hypodermic entirely control the diuresis for a time. This may be only a pharmacological effect, but the probabilities are against such an assumption. In the third place it has been noted at autopsy that many of the clinical cases have been associated with pituitary tumors. Other cases of polyuria have appeared after fractures of the base, where it is possible that the posterior pituitary or the stalk was injured, or its vessels thrombosed. Other cases have appeared after syphilitic meningitis at the base has been diagnosed, and have greatly improved after antisyphilitic medication. When, therefore, the condition appears in cases with normal roentgen-ray pictures of the sella one is to some extent justified in feeling that the "burden of proof has been shifted to the negative," and that some circulatory of "functional" disorder of the pituitary, though undemonstrated, nevertheless exists in all the true cases of this disorder.

Yet there are gaps in the theory, for there are not a few cases of pituitary and stalk tumors where polyuria is absent.

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[1] Loc. cit

Symptoms.—These have already been stated in a general way. The urine is profuse in amount, and frequent micturition is due not to irritability of the bladder, but exclusively to the immense volume of water. The twenty-four hours' amount may run as high as 25 or 30 quarts. The urine runs continually, day and night. Analyses present no special feature except lack of color and weight. When the specimen is still warm the specific gravity is often less than 1000. There is no albumin and no glucose. The reaction is normal. Estimates of urea and uric acid eliminated in twenty-four hours have shown no serious deviations from normal.

The kidneys seem to present no abnormality. Salts and sulphonephenolphthalein are eliminated as usual. An excess of salt (NaCl) by mouth is rapidly eliminated (Bailey and Bremer[1]). The blood-pressure is unaltered. The blood sugar is normal. A recent patient of mine, two hours after a lunch of mixed food, had 0.11 per cent of glucose in the blood. The same patient (adult, aged forty years) had a basal metabolism of −0.5 per cent. In a case reported by Langdon Brown[2] glycosuria induced by injection of phlorhizin appeared and disappeared normally.

Bailey and Bremer[3] claim to have observed in experimental animals that after the perivascular sympathetic nerve fibers to the kidneys are destroyed, the diuresis is temporarily greater (sympathetic diuresis), but returns presently to the grade of polyuria existing before the sympathetic nerve fibers were cut, thus indicating that the polyuria is independent of nervous influences.

Extreme thirst is a character of the disease. When fluid intake is restricted the outgo exceeds the intake and thirst is increasingly tormenting.

The *onset* of the disease is often so gradual that the patient does not realize for a time that anything is wrong with him. Sudden onset, after a fright, an injury, or an acute infectious disease, has also been noted. In those grave cases associated with tumor of the brain, the appetite is, of course, affected, but the patients with a benign form of the trouble eat heartily, and are incommoded only by thirst and an overflowing bladder. Sweat and saliva may be diminished; the skin is sometimes dry. "Cases have been known in which the tolerance for alcohol has been remarkable, the patients drinking a couple of pints of brandy or a dozen or more of bottles of wine in the day" (Osler).

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[1] Loc. cit., p. 165.

[2] Sympathetic System in Health and Disease, 2d ed., London, Henry Frowde, 1923, p. 46.

[3] Loc. cit.

Diagnosis.—The diagnosis may be usually made from the considerations already set down under Etiology and Symptoms. The low specific gravity of the urine, and the constant absence of glucose, with normal figures for blood sugar, perfectly well exclude diabetes mellitus.

Prognosis.—The prognosis depends on the precise character of the cause which is probably at work. Tumors and cysts of the gland and stalk are, of course, conditions of great gravity. The benign cases live for years, and finally die only of intercurrent disease. Spontaneous recovery sometimes is noticed. The prognosis is more favorable when syphilis is the cause, if diagnosis and treatment are prompt.

Treatment.—A careful search for the cause should be made. Roentgen-ray photographs of the sella are invaluable. The eye backgrounds should be carefully studied, and peripheral palsies of the external ocular muscles looked for. Langdon Brown[1] thinks syphilitic meningitis of the base of the brain the commonest cause. If it be reasonably suspected, or if the Wassermann reaction be positive, heroic doses of antiluetic remedies should be tried; but one should not, of course, forget that though the patient may have syphilis, the cause of the polyuria may be something else. Roentgen-ray photographs of the sella are sometimes entirely negative. In such cases, as has already been observed, one still has some justification for suspecting a "functional" disorder.

Medication.—The polyuria is immediately relieved for a few hours by hypodermic doses of 0.5 to 1 cc. of pituitrin. This effect fails so rarely as to suggest that reported failures happened with cases not properly diagnosed. The patient will soon tire of this troublesome and expensive mode of treatment, however. If he be a chronic *habitué* of free clinics he will presently fail to keep his appointment, and be heard of in a few months at another clinic. H. L. Blumgart[2] has found that by using pituitrin in larger doses (1 to 5 cc.) as a nasal spray the patient can get temporary relief. Other clinicians say that this may or may not succeed. Oral administration of pituitrin is ineffective. This fact seems to be established by clinical reports from many observers. Other extracts of pituitary gland have been reported as given *per os* for polyuria, mostly with negative results. As the exact character of the extract was unstated, such reports are of little value. One author found "fresh glands" given at bed-time sufficient to procure the patient a quiet night.

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[1] Loc. cit.

[2] Arch. Int. Med., 1922, **29**, 508.

In one patient recently under my care for a short time a preparation of pars intermedia, made up as suggested in the section on administration, produced encouraging results. The tablets were given by mouth, a few every afternoon and evening, and the patient slept all night without rising. This line of treatment may prove practicable when the therapeutic details have been worked out on a number of patients. The writer wishes to state his own limited experience with strict reserve.

Valerian in large doses was recommended many years ago by the clinicians of the last century. Langdon Brown[1] has revived the treatment and has reported distinct symptomatic benefit from the use of it. Codeine and morphine have been recommended.

In chronic benign cases the patients usually get tired of prolonged medication, and readjust themselves as they may to the inconveniences of the situation, finding out, for themselves, how little drinking water they can get on with, eating freely of a mixed diet and maintaining for years a very fair state of general health and nutrition.

MIXED FORMS OF DYSPITUITARISM.

Etiology and Pathological Anatomy.—The etiology and pathological anatomy of mixed pituitary disease are in general similar to conditions previously described as occurring in the simpler forms of dyspituitarism. Tumors—in the sella, near it, or by indirect pressure affecting its circulation and function—are common causes. Bony deformities, vascular diseases and local inflammations are found. Chronic hydrocephalus may by pressure affect the nutrition and function of the pituitary as a whole or of one of its parts (Cushing). The larger the size of the tumor and the more extensive the area of inflammation, the greater the probability of the entire gland being affected. For further details previous paragraphs should be consulted.

Frequency.—The mixed cases (or cases at one time mixed) probably predominate in number. One may wonder indeed that all pituitary troubles are not at one time or other mixed, when one considers the intimate relation of the two lobes to one another and their peculiar situation.

Symptoms and Diagnosis.—The clinical study of these cases is interesting but full of difficulties. The gaps in positive knowledge are large, and in the absence of proved facts, medical imagination has rather yielded to the temptation to run riot.

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[1] Loc. cit.

Theoretically we may have four forms. Calling the anterior gland A and the posterior P, and assuming for the time that there are no toxic pituitary troubles, but only a possible increase or decrease of normal secretion, we shall have:

A+ and P+.
A+ and P−.
A− and P+.
A− and P−.

When it is remembered that the A+ element, as already explained, may in time and under special conditions become normal again, or minus, and that the effects of the previous condition may sometimes persist as organic marks after the cause has ceased to operate, one can easily imagine that such patients become something of a Chinese puzzle. In obscure pituitary cases extreme reserve is necessary. Clinical histories and necropsy reports are still to be studied and collated in large numbers before diagnosis can be more than premature and unauthorized assumption.

To summarize briefly the probable functions of each lobe, the anterior lobe seems to (1) promote growth of bones and soft tissues, (2) to sustain and speed up the gonads and (3) to be possibly essential in other and unknown ways in mammals to the maintenance of life (p. 172).

The posterior lobe modifies carbohydrate tolerance and the secretion of urinary water. When the posterior lobe is damaged the temperature falls, the fat increases and polyuria begins.

To what degree, if at all, mental physiology is activated by the pituitary as a whole, or by either of its lobes, is a question not yet admitting of exact answer.

The ingenious diagnostician may amuse himself with the assumption that when anterior lobe deficiencies are associated with emaciation and glycosuria, the posterior lobe is irritated and is oversecreting. But glycosurias are of very variable origin. Ordinary diabetes might be present. Hyperthyroidism might complicate the case. To infer positively that in such cases one has an A− and P+ combination would be far from justifiable by the clinical data. As Horatio remarks to Hamlet, "T'were to consider too curiously to consider so."

It would appear, also, that simple and mixed pituitary disorders are at times complicated by thyroid, gonad and adrenal dyscrasias, thus producing a pluriglandular syndrome. A discussion of the few available facts is given in Chapter XIII.

Again, many pituitary disorders—anomalies of growth (gigantism, infantilism), of weight (obesity), of urinary secretion (polyuria)

—are associated with *epilepsy* and with *organic disease of the brain* (idiocy and imbecility in children and insanity of various organic types in adults). In such cases it seems, from every point of view, more rational to assume that the secretory disorder is secondary, or that both mental and secretory signs are the effects of a common (organic) cause. Autopsy records often support this conclusion.

When adolescents of either sex, in addition to the known bony and metabolic disorders of simple dyspituitarism, present symptoms of mental aberration of various "functional" kinds, that is, aberrations without known cerebral organic basis, one must be conservative in his assumptions. It cannot be proved that the mental deviation is due to dyspituitarism. All the mental symptoms often attributed to dyspituitarism appear under other circumstances also. Simple insufficiency of both the pituitary lobes has often been observed without mental defect. The causal nexus between the two conditions is too largely a matter of assumption. The reported beneficial results of pituitary medication in such cases are not numerous enough nor convincing enough to override the myriad possibilities of error. The therapeutic effect, when present, is apt to relate primarily to the growth and metabolism, and only secondarily to the mentality of the patients. I do not say that the relation is an impossible or even improbable one. I say only that it is *unproved*, and that unproved assertions are not more helpful to the advance of endocrinology than they are to any other science.

Treatment of Mixed Cases. Treatment of mixed cases must be based as usual elsewhere upon a search for the cause and an effort to relieve the symptoms. When the symptoms are apparently due to glandular deficiency opotherapy is a rational resort (p. 203). However, many of the patients are idiots, imbeciles and organically insane people already confined to institutions of various sorts; and treatment is mostly a matter for academic discussion. The medical practitioner is not a thaumaturgist.

Simmonds' Disease. For lack of a better place it seems proper to mention in this connection the strange phenomena of *Simmonds' disease* (*hypophyseal cachexia*). This clinical syndrome, described first by M. Simmonds,[1] of Hamburg, seems to be a distinct disease associated with a subacute degenerative lesion of the anterior lobe of the pituitary gland. Perhaps the posterior lobe is sometimes secondarily affected (polyuria?). The main impression made by the patient is that of premature senescence (senile cachexia). The hair rapidly grows gray, wrinkles appear upon the face, the body tissues waste, secondary anemia supervenes, and somnolence, mental depression, apathy and collapse are observed. There is loss of axillary and pubic hair, and a more or less complete sexual involution results.

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[1] Deutsch. med. Wchnschr., 1914, No. 7; 1916, No. 7.

Autopsies carefully made by competent pathologists have shown subacute inflammatory or degenerative changes in the pituitary gland as the only finding.

Besides the extreme cases noted above milder attacks have been recognized in which the trouble began and progressed in the same characteristic way, but more slowly and with less violent effects.

Diagnosis.—The diagnosis can be made from the symptoms *intra vitam*, though but few clinicians in this country are as yet familiar with the condition, which was first described when the World War was in progress.

Treatment.—Treatment is not always hopeless. One patient of E. Reye,[1] a woman of child-bearing age, improved immensely on fresh gland therapy in all regards except that the *crines pubis et axillarum* failed to reappear, and the atrophy of the sex organs persisted.

The essential chemical pathology of this condition—whether it is a hypopituitarism or a toxic pituitarism, whether the posterior lobe is involved or not—is very vague, and speculation is unprofitable without known data to reason from.

PITUITARY PHARMACOLOGY. THERAPEUTICS. DOSAGE.

Raw Material.—For therapeutic purposes bullocks' glands are generally used. As a counsel of perfection, in order to avoid the possible effects of castration on the pituitary, the glands of bulls and cows should be preferred. But there is no question that specific clinical effects can be got from bullocks' glands.

Preparations and Extracts.—*Anterior Lobe.*—Note has been already made (p. 159) of the unconfirmed claim of T. B. Robertson, that a lipoid of therapeutic value (*tethelin*) can be extracted from the anterior lobe. I do not know that it is to-day at all in use. The United States Pharmacopœia does not recognize any preparations of the anterior lobe. The preparations in common clinical use are mentioned in a later paragraph.

Posterior Lobe.—As *Hypophysis Sicca,* Desiccated Pituitary Body, Desiccated Hypophysis, the United States Pharmacopœia of 1916 listed the "posterior lobe obtained from the pituitary glands of cattle, cleaned dried and powdered." The dose is given as $\frac{1}{2}$ grain. The Pharmacopœia of 1926 (Tenth Decennial Revision) changes the name to Pituitarium (Latin), Pituitary (English), and gives the official abbreviation as Pituitar. The dose is the same.

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[1] Deutsch. Ztschr. f. Nervenheilk., 1921, **68-69**, 153.

Liquor Hypophysis (U. S. P. IX), Solution of Hypophysis, Solution of the Pituitary Body, is also listed in the Tenth Revision as Liquor Pituitarii (Latin), Solution of Pituitary (English), and the official abbreviation is Liq. Pituitar.

Directions are given for the preparation of a Standard Powdered Pituitary. In quantitative solution this has a definite effect on the contractions of relaxed virgin guinea-pig uterus. New solutions to be tested are compared with the standard solution. For the elaborate details the original account may be consulted. Dose, 1 cc., or 15 minims.

Liquor pituitarii is prepared and sold by the dealers under various trade names, such as pituitrin, infundin B. W. (formerly vaporole B. W.), glanduitrin, hypophysin, hypophysinum sulphuricum (Hoechst), pituglandol, etc. Blair Bell,[1] in 1909, suggested the name infundibulin. All these preparations contain an admixture of substances, for the posterior lobe extract has not been isolated and identified as a definite crystalline compound. Some dealers also add an antiseptic. One or the other of these facts may explain the varying physiological effects of some of them as compared with others.

The pharmacological and physiological actions of liquor pituitarii have been discussed on page 169. Its clinical uses are noted on page 206. Whether the physiological action of the posterior lobe is *limited* to this substance is unsettled.

Therapeutic Medication.—Therapeutic medication with *whole gland* and with *anterior lobe* has been mainly confined to the use of fresh glands, frozen (cold storage) glands, and desiccated gland substance.

Freezing the glands evidently invites decomposition and autolysis. The use of fresh glands is inaccurate, uncertain and when the patient is at a distance from an abattoir impossible. Desiccated gland is the least objectionable resource, but commercial processes usually include treatment with a fat solvent, which extracts not only the ordinary fatty acids, but the cell lipoids as well. Preparations of fresh whole and of anterior and posterior gland dried rapidly in the cold, and untreated with fat solvents have been recently put on the market by several New York dealers. They attempt no standardization except weight, so much dried powder being equivalent to so much fresh gland. This preparation is coming to be recognized as a distinct advance on older methods, and must serve until exact chemical studies have thrown more light on the precise nature of the active principle, or principles, that are probably present.

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[1] Loc. cit., p. 160.

When oral administration fails, or from the nature of the case is impracticable, *hypodermic preparations* have to be considered. As little or nothing is known of pituitary lipoids, as good a resource as any is the nucleoproteid precipitate, which carries down by *adsorption* a large part of the solid matter in the gland. It should be collected, washed, dried, weighed and run through a clay filter after quantitative re-solution. Faintly alkaline saline solutions of the whole gland, or of either part, may be used after Berkefeld filtration. Such preparations keep for a few days. Autolytic processes after that time may cloud them. Cushing reported that boiled extracts of anterior lobe will affect favorably the subnormal temperature of some operative cases (p. 171).

The ordinary commercial powders vary deplorably in potency. Some seem to be entirely inert. Cushing and his associates have described the giving of enormous doses *per os*, sometimes as much as 200 or 300 gr. per day. Inasmuch as the gland of a 2000-pound bullock when fresh weighs only about 30 gr., and when dried only about 3 or 4 gr., one can only presume that in such cases the material was inert, or that absorption by stomach and bowels had largely failed. When pituitary preparations are made in the manner I have above suggested, a few grains a day, in split doses, to properly selected cases, are usually enough to elicit a therapeutic response. If the case is urgent, or smaller doses have failed, larger amounts involve no particular danger. There is no question, I think, that anterior pituitary *is* absorbed from the alimentary canal. To be sure of covering all the metabolic possibilities of the posterior lobe, it is well to give posterior lobe powder by mouth and a few doses of liquor pituitarii by hypodermic every day besides.

Specific Indications.—The specific indications for pituitary medication are those of hypopituitarism of any kind. The presence of diabetes insipidus seems to be a specific indication for liquor pituitarii.

There are a number of other clinical uses of pituitrin and of pituitary extract, which may be related to specific uses, but are essentially pharmacological. I classify them therefore as *clinical uses.*

SYMPTOMATIC CLINICAL USES OF PITUITARY GLAND.

Liquor Pituitarii.—Liquor pituitarii is of value as an *oxytocic.* The powerful effect of posterior lobe extracts on uterine and other smooth muscle was noticed early in the laboratory study of the gland. Such a use is also in a measure suggested by the hyperplasia which the gland (anterior certainly, and probably posterior, too) undergoes during pregnancy. The value and limitations of the extract in obstetrics are well summarized by J. C. Hirst[1] (condensed quotation):

"Liquor hypophysis is the best of all oxytocics. Its action on the uterine muscle is greatest in labor; less when used to induce labor; as an abortifacient entirely unreliable. It should be given in primiparæ only when the head has passed through the cervix; in multiparæ only when the cervix is fully effaced; it should never be given when there is an obstacle to easy delivery. Half a cubic centimeter is a full dose. This should be injected into a muscle, never into a vein. An overdose will be followed by relaxation and hemorrhage. In syphilitic patients liquor hypophysis is dangerous; uterine rupture may occur.

"Besides rupture the general dangers in all patients are *post-partum* hemorrhage, fetal asphyxia, cervical tears from precipitate delivery, and premature separation of the placenta."

Blair Bell[2] thinks it of great value in *Cæsarean section* as a means of securing prompt contraction of the uterus after delivery of the child. He also commends it as a useful symptomatic remedy in *menorrhagia* and in the *gastric* and *intestinal atony* following surgical operations.

As a temporary corrective of *low blood-pressure* it is used alone and in combination with epinephrine.

Contraindications.—Besides the contraindications already mentioned in obstetric practice are to be mentioned essential hypertension, old Bright's disease and cardiac dilatation. Some commercial preparations seem to be harmful in bronchial asthma. For this trouble it is safer to use epinephrine alone. Asthenia and pallor have been mentioned as following its continued use in diabetes insipidus, possibly from imprudent dosage. Krabbe[3] mentions that continued use of it promotes hypertrichosis. I never noticed any such effect myself.

Whole Pituitary Gland.—Whole pituitary gland had quite a vogue at one time (as indeed one-half the remedies in the United States

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[1] Manual of Obstetrics, 2nd ed., Philadelphia, Saunders, 1924.

[2] Loc. cit.

[3] New York Med. Jour., July 6, 1921.

Pharmacopœia have had in their day) as a "cure" for *idiopathic epilepsy*. The literature of ten years ago was quite favorable. I believe the practice nowadays has died a natural death, though some of the manufacturers still try to galvanize the corpse. Its only apparent rational use is in such cases of epilepsy as complicate a non-hyperplastic tumor of the pituitary gland, or a compressive tumor outside the sella.

Persistent somnolence has been treated with whole pituitary. It is true that abnormal sleepiness is a symptom of some pituitary disorders. Calcification of the pituitary has been described (p. 175) as marked by this symptom, and one reported case was apparently relieved entirely by opotherapy. But there are many other causes of somnolence. A notion of the extent of the subject may be got from the interesting study by C. L. Dana,[1] who reviews the relations of somnolence to brain tumors in general, and to endocrine disturbances.

Menstrual migraine is said to be relieved by giving pituitary. The *rationale* is supposed to exist in the fairly well-established fact that the pituitary, like the thyroid, swells during menstruation. In laboratory animals observed before, during and after œstrus the fact has actually been noted. Giving pituitary extract, therefore, presumably relieves the strain on the capsule due to congestion of the gland. It is difficult, however, to find in the literature any carefully reported cases of cure, with accurate details of the previous history of the attacks, and a statement of other remedies simultaneously employed. "Menstrual migraine" generally is merely an an attack of ordinary migraine precipitated by the menstrual nisus, as it may also be by overeating, eye-strain, prolonged loss of rest, or a period of painful excitement.

Delay in the menarche in young girls, and in older women *premature amenorrhea* (in men *impotence*) when these conditions are not demonstrably associated with organic lesions of the genitals or gonads, have been treated with pituitary extract. The reason is found in the facts that hypopituitarism is often associated with gonad involution, and that normal œstrus is accompanied by pituitary swelling. The clinical results have been conflicting. Some of the failures might naturally be attributed to errors of diagnosis (particularly an unrecognized coincident hypothyroidism), some to inertness of the medicament used. Some of the reported cases received only liquor pituitarii *per cutem*—a form of treatment which some physicians still think means the same as giving whole pituitary.

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[1] Med. Rec., 1916, **89**, 1.

Pituitary headache, as a clinical symptom occurring alone, in either sex, has been described by I. H. Pardee.[1] He thinks it too infrequently recognized. He believes that it is due to simple hyperplasia or struma of the gland, and reports a number of cases wonderfully relieved by pituitary medication. He seems to have used commercial whole gland. Many of his cases were studied by roentgen-ray, and the photographs quite often showed some sellar abnormality.

Contraindications for whole pituitary medication are in general merely the clinical signs that the gland is already too active. I know of no alarming or dangerous signs from overdosage *per os* of whole gland. The dangers of liquor pituitarii have been already noted.

[1] Arch. Int. Med., 1919, **23**, 174.

CHAPTER VII.

ADRENAL GLANDS. CHROMAFFIN SYSTEM.

Adrenal Glands.—The adrenal glands (*Nebennieren, Glandes Surrénales*) are also known as *Suprarenal Glands*, or (in the older anatomical works) *Suprarenal Capsules.* The name merely relates to their position, cephalad to the kidneys. Owing to the brownish color of the cut surface of the medulla, they were once called the "atrabiliary capsules."

Chromaffin Bodies.—The chromaffin (Kohn) bodies, which are also called *Chromophil* (Stilling), *Chromaphil* (Vincent, after Schaefer) and *Phaeochrome* (φαιός, dark, after Poll) are collectively known as the *Chromaffin* or *Chromaphil System.* The name refers to their generally distinctive quality of turning brown with aqueous solutions of chromium salts.

Historical.—A. Biedl[1] has collected some diverting anecdotes relating to the history of these bodies. P. Langlois[2] also gives historical notes. It was at one time supposed that the late Latin word *renunculus*, diminutive of *ren*, kidney, appearing in the Vulgate Scriptures (Lib. Levit., vii, 3. "Offerent ex ea [victima] caudam et adipem qui operit vitalia: 4. duos renunculos et pinguedinem quae juxta ilia est, reticulumque jecoris cum renunculis.") indicated that the ancient Hebrews were acquainted with the adrenals. Later criticism has shown this word to be a mistranslation of the Hebrew original.

As commonly stated, the adrenals were first described by Eustachius in 1563.

Next to the thyroid there are few subjects in animal physiology which have attracted more interest, and none that has proved more baffling than the adrenals. The famous papers by the English physician, Thomas Addison,[3] first describing the disease of the adrenals still known by his name, and the discovery, by Oliver and Schaefer,[4] of a blood-pressure-raising principle in the medulla of the gland, are the epoch-making facts. The proved existence of this pressor principle furthers plausible conjecture as to the function of the medulla, but the cortex has so far defied analysis. Its secret has not been "wrung from Nature's close reserve" even after years of patient and ingenious study, and after the accumulation of a fairly mountainous literature. The imperfectly correlated inferences to be drawn from autopsies and from tumors of the gland are assembled in later sections of this Chapter.

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[1] Loc. cit.

[2] Loc. cit., p. 226.

[3] London Med. Gaz., 1849, **7**, 517; Constitutional and Local Effects of Disease of the Suprarenal Capsules, London, 1855, with beautiful quarto atlas of colored plates.

[4] Jour. Physiol., 1894, **16**, p. i, Proceedings; 1894–1895, **17**, p. ix, Proceedings; 1895, **18**, 230.

ANATOMY OF THE ADRENAL GLANDS.

Gross Anatomy.—In the human subject the adrenals are two in number, yellowish in color, symmetrically situated in the abdomen behind the peritoneum and just in front of the upper end of either kidney. The right adrenal is somewhat triangular in outline, "like a cocked hat;" the left is rather semilunar. The left is larger and higher than the right. They are sometimes so small as almost to elude the eye; generally they are 4 or 5 cm. in length, rather less than this in width and about 0.5 cm. in diameter. Each weighs in the adult male from 1.5 to 2.5 gm. The right adrenal is behind the under surface of the liver; the left is in relation with the spleen and pancreas. Cross-section shows from without inward a fibrous capsule, sending trabeculæ into the organ, a *cortex* of rather firm yellowish columnar masses of cells, and a *medulla*, or marrow, which is pulpy, bloody and in color dark brown or black (Fig. 37).

Accessory Adrenals.—These are: (1) *Accessory adrenals proper*, containing both cortex and medulla; (2) *accessory cortical tissue;* (3) *accessory medullary tissue.*

Accessory Adrenals Proper.—Like accessory thyroids or thymuses, accessory adrenals proper are theoretically to be found anywhere in the neighborhood of the principal glands. Their number and size are variable both in species and individuals. In experimental animals they have obviously a vital relation to the results of adrenalectomy. On section cortex and medulla are anatomically similar to the same parts of the principle glands. Biedl[1] affirms that their reported occurrence in adult man is extremely rare. However, this may be due to lack of special studies in this direction. Gray[2] states they are not uncommon.

Accessory Cortical Tissue.—Accessory cortical tissue has a histology notably like that of normally situated cortex, and contains no medullary cells at all. Masses of this structure may be 1 cm. in thickness, or so small as to be identifiable only with the microscope. Marchand,[1] with whose name some of them are still sometimes coupled, Pilliet and V. Veau,[2] Eggeling[3] and many others have reported them in all sorts of curious places. They may be discrete particles lying around the upper poles of the kidneys or in the retroperitoneal space. They may be found included in the capsule or parenchyma of other organs, *e. g.*, in the liver, the broad ligaments, the testes (probably migrating with these organs), between testis and epididymis, along the vas deferens and in the cortex or medulla of the kidney. These various unexpected locations suggest a developmental anomaly, a derivation from cells or cell masses aberrant from the primitive anlage, and this view is very generally held. Some malignant hypernephromata are thought by various authors to derive from cortical adrenal cell masses aberrant in the kidney (p. 229) or elsewhere.

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[1] Loc. cit.

[2] Anatomy, 21st ed., Philadelphia, Lea & Febiger, 1924.

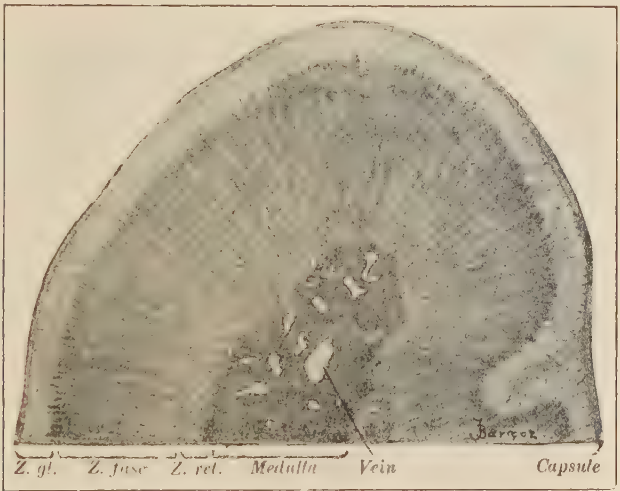

FIG. 37.—Cross-section of adrenal of dog. *z. gl.*, zona glomerulosa. × 22. (Szymonowicz.)

Accessory Medullary Tissue (The Chromaffin System).—The chromaffin bodies, which are now generally viewed as accessory to the adrenal medulla, were first noticed in mammals by H. Stilling.[4] He called them *chromophil bodies* and described them as follows:

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[1] Virchow's Arch. f. path. Anat., 1883, **92**, 11.

[2] Compt. rend. soc. de biol., 1897, 10. Ser., iv, 64.

[3] Anat. Anz., 1902, **21**, 13.

[4] Rev. d. méd., 1890, **10**, 808.

"Henle first noticed that the adrenal medulla shows up brown with bichromate of potassium. . . . I have noted for some years that certain small bodies around the great sympathetic ganglia of the abdomen take the same coloring. Their form and size vary. They may be 1 cm. thick; they may be hardly visible to the naked eye. They are round, oval or oblong. They may not be more than several millimeters in thickness. . . . Their microscopical structure is exactly that of the adrenal medulla. I have found them in cats, rabbits and dogs, and never failed to find them. They may be very numerous; in one cat I counted 30. . . . They are hard to find in man because the [chrome] reaction fails completely twelve hours after death. . . . These are evidently the 'paired bodies' (p. 214) which Balfour found in Elasmobranchs."

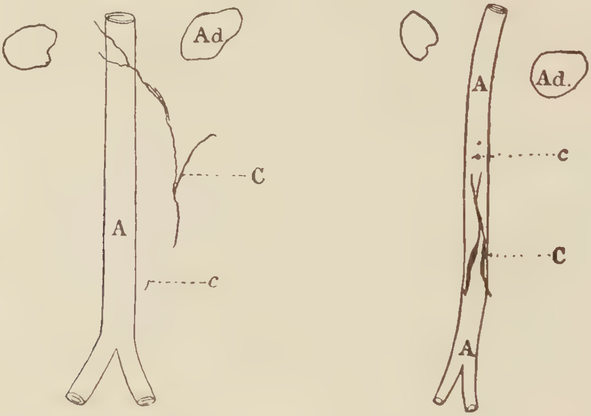

FIG. 38.—Abdominal chromaffin bodies. Left, adult cat; right, rabbit. *A*, aorta; *ad.*, adrenal; *C.*, large, and *c.*, small chromaffin masses. (From Swale Vincent's Internal Secretions and Ductless Glands, Arnold, London, 1924.)

This was the beginning of our knowledge of the chromaffin system. Further historical references may be found in the accounts of Vincent and Biedl. The chromaffin bodies may be easily shown by laying a mass of cotton soaked with potassium bichromate (5 per cent or thereabouts) on the freshly removed abdominal tissues of any convenient animal. Staining is evident in an hour or two; six to twelve hours is long enough for a good result. Washing in running water should follow, after which they are best placed in glycerin (Vincent). Chromaffin tissue occurs also in long strings and irregularly thickened bundles running across or along the aorta (Fig. 38).

Histology.—The *cortex* of the large glands shows a *capsule* of fibrous tissue. Next within this is found a clump layer (*zona glomerulosa*), then a bundle layer (*zona fasciculata*), then a network *layer* (*zona reticularis*) of cells. The figures adjacent explain themselves (Figs. 39 and 40).

Within the cortex, closely apposed to it, and separated only by a fine line of connective tissue, comes the *medulla*. This consists of large chromaffin cells arranged in a connective tissue network which carries in its meshes large venous sinuses. The histology of the accessory glands proper, of the cortical and the medullary accessory tissues is so closely similar to that of the corresponding parts of the principal glands, as strongly to indicate identity of function.

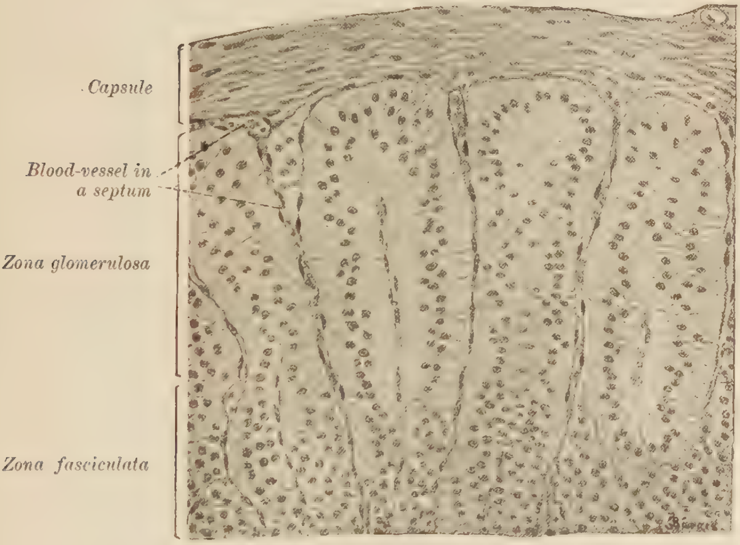

FIG. 39.—Cortical substance. Adrenal of dog. × 245. (Szymonowicz.)

Circulation.—The arteries of the adrenals are numerous. They arise from the aorta directly, and from the renal and inferior phrenic arteries. The veins present no special features. The suprarenal vein on the right side empties into the inferior vena cava, on the left into the renal vein. The lymphatics appear to end in the lymph nodes of the lumbar region.

Nerves.—The nerves of the principal glands and of the chromaffin system are derived from the sympathetic. They are said to be both vasomotor and secretory. The parasympathetic has no known connection with the adrenals.

Comparative Anatomy and Embryology.—Within the space limits of this volume only a brief outline can be attempted. All recent writers on the subject acknowledge their debt to the exhaustive studies of Heinrich Poll.[1] In the Anamnia a number of small and scattered bodies homologous with the adrenals of higher vertebrates can be demonstrated. The arrangement in fishes is peculiar. F. M. Balfour[2] remarks (condensed quotation): "In Scyllium (dog fish) two structures have gone under the name of the suprarenal body. One of these is unpaired, rod-like, lying between the dorsal and caudal vein near the rear end of the kidneys. This I

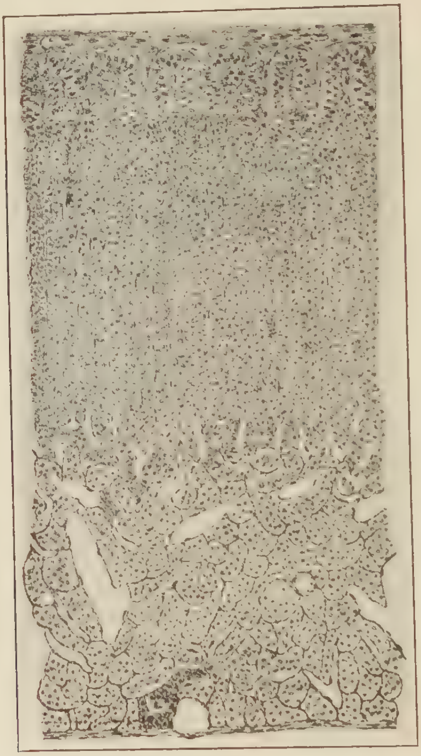

Fig. 40.—Section of adrenal cortex and medulla, adult dog. × 150. (Flint.)

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[1] Hertwig's Handbuch d. Entwickelungslehre d. Wirbelthiere, 1906, **3**, 443, with references.

[2] Monograph on The Development of Elasmobranch Fishes, Macmillan, London, 1878.

propose to call the *interrenal body*. The other is formed by a series of paired bodies segmentally arranged dorsal to the branches of the aorta (Fig. 41). . . . The interrenal body seems to

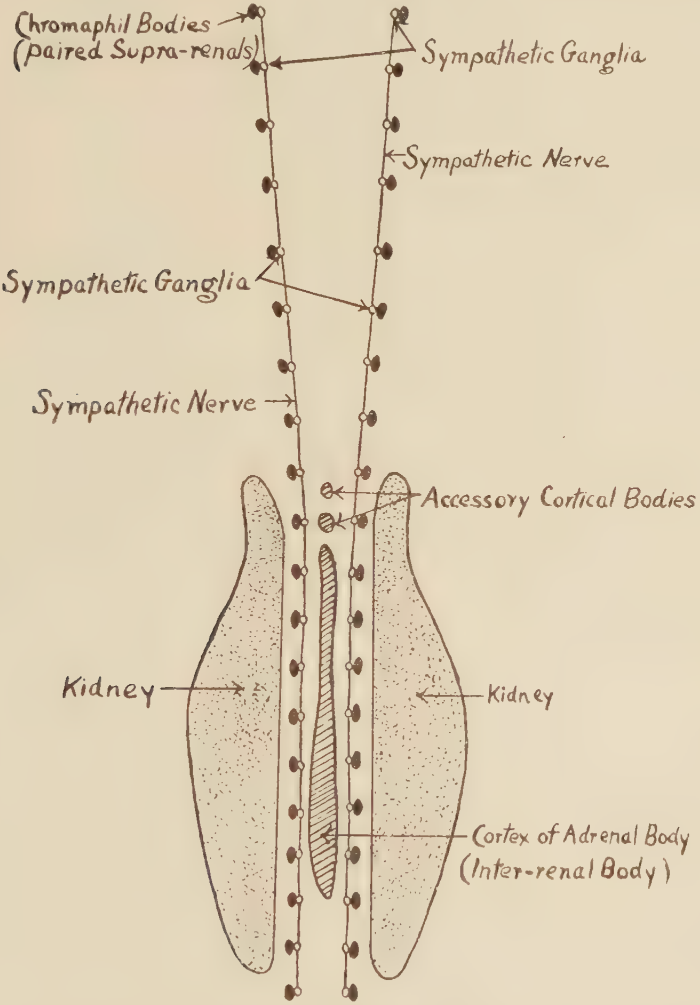

FIG. 41.—Diagram of adrenal representatives in Elasmobranch fishes, showing cortical (interrenal) bodies, chief and accessory, and the "paired" chromaffin bodies in relation to the kidneys and sympathetic. (From Swale Vincent's Internal Secretions and Ductless Glands, Arnold, London, 1924.)

develop from mesoblast; the suprarenal or paired bodies appear to me also, as first supposed by Leydig, to be formed out of the sympathetic ganglia."

Interrenal bodies near the kidneys in bony fishes (Teleosts) were first noted by Stannius,[1] and were long called "corpuscles of Stannius." Later important work by Pettit, Swale Vincent, Ecker and Diamare is reviewed in an interesting study by E. Giacomini.[2] In adult eels (Anguilla) Giacomini found not only posterior interrenal bodies (two as a rule), but an anterior system as well, located further along the vertebral column in the thorax. In Amphibia (Poll[3]) the adrenal and interrenal bodies approach closer to each other. In birds they interlock. In mammals they form a compound organ within one capsule.

Balfour's and Leydig's conception of the embryological origin of the two structures has been generally confirmed. The interrenal body arises from mesoblast (cœlomic epithelium); the adrenal system arises from the same structures that make the sympathetic nervous system, *i. e.*, the neural ectoderm.

The marked effect of medullary extract on the action of the sympathetic fibers (see later sections) has therefore an anatomical substratum of relationship, which may be of some consequence.

Since Balfour's time it has become the general custom in zoölogy to call the unpaired homologue of the mammalian adrenal cortex the interrenal body (*Zwischenniere*); and the entire cortical system in man and mammals is also called by some writers the *interrenal system*.

Poll's summary of the facts of comparative anatomy is interesting. He calls attention to the "fish stage" as the first known association of the two bodies. "The second step is the placing side by side of interrenal and adrenal bodies (Amphibia); the third is the interlocking of the two tissues (birds); the fourth and last, to which only the mammals attain, culminates in the complete envelopment of the chromaffin by the interrenal component. And the mammalian ontogeny is not a slavish reproduction of the phylogeny, but an arrangement which is only suggestive."

The same author[4] believes it may be inferred from the facts of experimental adrenalectomy that after excision of the two large glands a mammal will not live, however abundant its supply may be of accessory cortical and of accessory medullary tissue (chromaffin substance). To preserve life a complete accessory gland must be present—one with cortex and medulla in contact. This is a plausible conjecture not yet scientifically proved.

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[1] Müller's Archiv, 1839.

[2] Mem. r. accad. d. sci. d. ist. di Bologna, March 24, 1908, with references.

[3] Loc. cit.

[4] Loc. cit.

Adrenals in Laboratory Mammals.—A separate description is not needful. The facts just mentioned in this chapter as true for man are mostly duplicated. In number, size and occurrence the accessory glands are as variable as in man, and this variability is a troublesome unknown quantity in interpreting the results of experimental excisions. Biedl states that, in general, complete accessory glands are very common in rats (50 per cent); rarer in rabbits (15 to 20 per cent); extremely rare in dogs and cats and guinea-pigs. In rats, therefore, survival after double ablation is much more often to be expected.

PHYSIOLOGY OF THE ADRENALS.

A. Cortical Tissue. -The physiology of the cortical tissue is very imperfectly understood. Many clinicians have been so much absorbed with the known facts of the medullary secretion that they have almost ignored the function of the cortex. Indeed, one wonders after laying aside some recent enthusiastic papers whether the writers knew that there is such a thing as adrenal cortex.

Excisions.—The lower animals in which it exists as an accessible organ in a separate place are too far removed from mammals in the zoölogical scale to make *excision experiments* (of the interrenal body only) very significant. In mammals it has been boldly proposed to cut away the cortex and leave the medulla, or *vice versa*, but this operation damages the blood supply of the remnant irreparably, and results reported by various writers are of questionable value. The existence of complete accessory glands, and the possible vicarious action of discrete interrenal and chromaffin bodies further obscure the question. A short summary, however, must be given of the ingenious, patient and laborious work of the many experimenters in this field.

In eels Pettit[1] and S. Vincent[2] removed the interrenal bodies. Pettit removed one only, and reported that the subjects survived with hypertrophy of the gland remaining. Vincent in a series of experiments removed two posterior glands, not then knowing of the accessory anterior interrenals present in these animals (Giacomini[3]). Vincent's subjects recovered. Biedl[4] operated upon 32 Rajidæ (ray and torpedo fish), removing the interrenal system completely. Some of the animals died promptly from defective technique; 5 that survived permanently had hypertrophic remnants accidentally left behind at operation; all the rest died in two or three weeks with symptoms of "general prostration."

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[1] Compt. ren. soc. d. biol., 1896, p. 320.
[2] Loc. cit.
[3] Loc. cit., p. 216.
[4] Loc. cit.

With cats and dogs Biedl also claimed that in fractional removal ("amputation") of the glands survival might be expected if as much as one-eighth of the original cortical tissue was left. This he managed by removing one gland *in toto*, curetting out the medulla from the other, and leaving part of the cortex. It goes without saying that this is a rather violent procedure—nerves and blood supply must be badly damaged. This author gives references and abstracts relating to later work.

With due reservations, it may be said that the bulk of experimental evidence favors the view that the cortex is essential to life, but in what way has not been more than guessed at.

Evidence from Autopsies.—Tumors of the adrenals other than hyperplasias throw but little light on the physiology of the cortical glands. Bilateral cysts have been associated with Addison's disease, but cysts destroy, or may destroy both cortex and medulla. Hypernephromata of adrenal origin (aberrant cortex) are said to be unaccompanied by anything except the common signs of pressure and malignancy associated with all tumors (p. 229). In some cases of feminine pseudohermaphroditism in girls and women autopsy has revealed a hyperplasia or adenoma of the cortex of a chief gland. This curious concurrence of tumor and symptom-complex is discussed elsewhere (p. 289).

There is some ground for the view that deficiency of the cortical secretion is responsible for the pigment deposits in Addison's disease (p. 227).

Chemical Studies.—Chemical studies of the cortex have shown the presence of the usual organ proteins, of lipoids and tissue extractives. Repeated tests have failed to show more than a trace of the pressor principle characteristic of the medulla. In animals dying after total adrenalectomy injections of saline suspensions of the whole gland, and of all varieties of extracts of cortex and medulla have failed to preserve, though they have been reported to prolong life. The question here is similar to the year-long problem of the pancreas—a problem only recently brought to a successful solution by Banting and Best with the discovery of insulin.

Organotherapy.—In Addison's disease organotherapy throws some helpful light on the nature of the cortical principle, but there are many gaps in the evidence (p. 233).

B. Medullary Tissue.—Chemical Studies.—As to the function of the medulla the discovery of Oliver and Schaefer[1] holds the first place. These authors give a short synopsis of previous studies, with references. Their most efficient extracts were made with water. They found alcoholic extracts inert. They used the glands of calves, sheep, guinea-pigs, cats and dogs. They found invariable evidences of a pressor principle. This was discovered to exist in the medulla only. Boiling for a short time did not injure it. In dogs subcutaneous injections of the extracts were only temporarily depressing; in rabbits death occurred. These phenomena were unexplained, but it was noticed in all tissues of all animals injected that there was a prompt and powerful contraction of the arterioles; that this was due to a direct effect upon the smooth muscle of the arterial walls, and that in animals otherwise normal, there was a prompt and very high rise in the blood-pressure. Respiration and secretion were not materially affected. The pressor effect was far in excess of that produced by much larger relative amounts of digitalis and ergot.

Extracts made from diseased adrenals removed at autopsy from a case of Addison's disease were inert.

Peptic digestion, a short period of boiling and treatment with acids had no damaging effect. Prolonged contact with alkalies was damaging. The active principle, they thought, was identical with a substance obtained by Vulpian,[2] which gave a rose-red color with exposure to air or oxidizing agents. (Vulpian remarked as to the function of this substance that "he dared not hazard a guess.")

Later researches in the next few years by Moore, S. Frænkel, von Fuerth[3] and J. J. Abel[4] narrowed the region of doubt as to the formula of this substance, and J. Takamine[5] isolated it in crystalline form. He named it *adrenalin*. Fuerth called it *suprarenin*, and Abel *epinephrine*. In the United States Pharmacopœia Abel's name has been recognized as official, perhaps by reason of its having no commercial implications. (But Stedman's Medical Dictionary says epinephrine is also a trade name). Independently of Takamine and almost at the same time T. B. Aldrich[6] also isolated epinephrine as a definite chemical substance.

Epinephrine.—Epinephrine is basic, rather insoluble in alcohol and readily soluble in hot water. It makes salts with acids.

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[1] Loc. cit., p. 209.

[2] Compt. rend. acad. d. sc., 1856, vol. **43**.

[3] Ztschr. f. physiol. Chem., 1897–1898, **24**, 142.

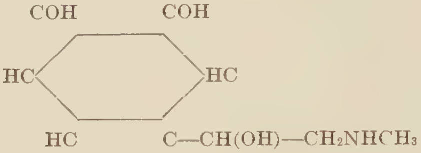
[4] Bull. Johns Hopkins Hosp., 1898, **9**, 215.

[5] Therap. Gaz., 1901, p. 221.

[6] Am. Jour. Physiol., 1901, **5**, 457.

Epinephrine chloride is readily soluble in cold water. Aqueous solutions of epinephrine turn red in air, green with iron chloride and red with iodine, nitric acid, gold chloride, potassium ferrocyanide and potassium bichromate. The crystals are colorless. They melt at 212° C.

Epinephrine has a benzol nucleus, and has the molecular formula (U. S. P.) $C_9H_{13}O_3N$. This has been analyzed structurally as a derivative of pyrocatechin of relatively simple structure—an amino-alcohol, *dioxyphenyl-methylamine-ethanol:*



This substance has, therefore, *two isomeric forms.* Both have been prepared synthetically. Only the *laevo* form appears in the adrenal medulla. The official designation of epinephrine by the United States Pharmacopœia is *laevo-methyl-amino-ethanol-catechol.*

Epinephrine goes under various trade names (p. 239). Genuine epinephrine is levorotatory. The quantitative estimate in solutions and the various color reactions have been studied by Johannessohn.[1]

Physiological and Pharmacological Action of Epinephrine.—Of this immense and important subject only an outline is possible.

To quote the valuable generalization of Langley (Chapter II), epinephrine has a stimulating effect specifically selective for all the ramifications of the sympathetic nervous system. It will produce the same effect upon all organs supplied by the dorsolumbar autonomic outflow as that following electrical stimulation of the sympathetic nerves.

Its mode of producing contraction in smooth muscle is summarized by W. E. Dixon,[2] as follows:

"It is quite clear that adrenalin cannot act on the nerve endings in the ordinary sense, *i. e.*, the terminal fibers as revealed by methylene blue, since tissues in which all the sympathetic nerves have been cut and allowed to degenerate, still respond to adrenalin, and are even supersensitive to it.

"Adrenalin certainly does not act on the contractile substance. The proofs in this case seem overwhelming. First, we can antagonize the effects of adrenalin, either the motor only (ergotoxin) or the whole effect (apocodeine), leaving the response of the muscle to mechanical and chemical stimuli intact. Secondly [there is] the established fact that the response of plain muscle to adrenalin is determined by the presence of a sympathetic nerve supply.

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[1] Biochem. Ztschr., 1916, **76**, 376, with references.

[2] Manual of Pharmacology, 5th ed., London, Arnold, 1921, p. 441.

"To meet these requirements the term *myoneural junction* has been employed, a tissue not necessarily being an integral part of either the nerve or muscle."

By German writers the myoneural junction is called the *receptive Zwischensubstanz* (Meyer and Gottlieb[1]).

Epinephrine has a tonic effect on the muscle of the heart and arteries. It raises blood-pressure. In the eye it retracts the membrana nictitans, protrudes the bulbus, opens the lid, whitens the conjunctiva and dilates the pupil. In the salivary gland in sufficient doses it increases the outflow of "sympathetic saliva." It erects the hairs of the cat and the quills of the porcupine. It contracts the pigment cells in the skin of a black frog, producing a light color. F. Blum[2] first announced the curious property of epinephrine by which subcutaneous and intramuscular injections (less perfectly intravenous injections) produce a hyperglycemia and glycosuria. This is believed due to its direct action on the cells of the pancreas which subserve the secretion of insulin (Herter and Wakeman[3]). The theory is further alluded to in other chapters.

The pressor effects of epinephrine are quite similar to those of pituitrin (posterior pituitary extract), but pituitrin acts more slowly and its effects are more persistent. Exact physiological differences between the two have not been worked out, but their pharmacological uses in practice have been highly differentiated. (See the respective Sections of this book.) B. A. Houssay[4] found adrenalin and pituitrin to act antagonistically on the smooth muscles of the bronchioles. He advised against the combination of the two in asthma, quoting from other authors the experience that pituitrin alone may even precipitate an attack of asthma. Abel, however, notes that commercial pituitrin often contains foreign substances which produce atypical effects.

Whether epinephrine and pituitrin coöperate in the maintenance of normal blood-pressure, and whether either of them is essential to this function, is at present a matter of controversy (p. 341). The effects of epinephrine upon the other glands of internal secretion are but little understood (Chapter XIII). To insulin it seems to be a physiological antagonist, and this is also alleged of its relation to secretin (Vincent).

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[1] Loc. cit., p. 241.

[2] Deutsch. Arch. f. klin. Med., 1901, **71**, 146.

[3] Med. News, 1902, **80**, 865.

[4] Presse méd., 1918, **26**, 513.

Upon the *temperature* of the animal body the effects of epinephrine, either alone or in conjunction with thyroid and the adrenal cortex, are uncertain. More exact studies of the dosage and manner of administration may throw more light on the subject. W. Cramer's[1] work is of interest. He stained with osmic acid fresh adrenal tissue of normal mice, mice exposed to cold and mice injected with fever-producing drugs; he thought it possible to show in this way that the adrenalin "load" of the medulla was reduced by the abnormal conditions mentioned, and he concludes that the adrenal medulla is excited by many different stimuli, of which "one connected with heat regulation of body is almost always operative." Similar stains of microscopic sections of thyroid gland showed like signs. "These observations support the conception that thyroid and adrenal glands regulate bodily heat." No mention is made of controls. The obscurity of the subject is further illustrated by the paper of D. Marine and E. J. Baumann.[2] These writers reported that partial destruction of the cortex of the adrenals with intact thyroids led to increased heat production. Removal of the thyroids prevented or lessened this. Their inference is that thyroid overaction follows upon insufficiency of the adrenal cortex.

Conclusions.—A cautionary note that must be added to the supposed "physiological" researches upon the effects of tissue extracts in general, and of epinephrine in particular, is that all such work is primarily pharmacological. In the present state of our knowledge it cannot be safely affirmed that adrenal medulla, or the chromaffin system, *in vivo* and *in situ*, perform a tithe of the functions indicated by injection experiments. The method of administration, the dosage, the animal used, the physiological condition of that animal, all offer unnumbered opportunities for error. When the final pharmacological residuum of confirmed facts is assembled, the physiological inferences are still largely conjectural. Among other students, Stewart and Rogoff[3] appear to have shown conclusively that after complete section of the nerve supply to the adrenals in experimental animals epinephrine is no longer present in the blood stream in amounts detectable by the most sensitive biological tests. Yet the animals seemed well, and lived indefinitely. They conclude that epinephrine is not essential to life. If this be so the actual service—the physiological service—that the medulla and the chromaffin bodies render to the animal organism is still something of a problem. This view is concurred in by Gley and Quinquaud[1] and R. G. Hoskins.[2]

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[1] Sixth Scientific Report Imp. Cancer Research Fund, 1919, p. 1.

[2] Am. Jour. Physiol., 1921, **57**, 135.

[3] Jour. Pharm. and Exper. Therap., 1917–1918, **10**, 1, with references.

Toxic Effects of Epinephrine.—These have been intensively studied by numerous writers. The extract is promptly fatal to dogs, rabbits and guinea-pigs in intravenous doses of 0.1 to 0.2 mg. Subcutaneous and intraperitoneal doses of about twenty-five times as much as this are borne. Larger quantities are fatal. In mice suitable doses produce death in convulsions at once, or collapse, stupor and a rapid fall of temperature, with death in a few hours. Smaller and less rapidly fatal subcutaneous doses are said to produce necrosis at the point of injection, and in distant organs hemorrhage, necrosis, fibrosis and degeneration.

An immense amount of study has been given to the toxic effects of epinephrine upon the *vessel walls of animals*, especially of rabbits. Josue[3] made the first comments. Even after a very few small intravenous doses atheromatous dots of a pin-head size appear on the inner coat of the aorta. These presently enlarge and become partly calcified. Degenerative changes proceed in the intima, muscularis and elastica. When small doses are continued long enough all the arteries are similarly affected. The results seem to be due to both toxic and hypertensional influences. Controls with a miscellaneous variety of other substances (not pressure-raising, hydrochloric acid, lactic acid, phlorhizin, pepsin, chloralamide) produced similar but not such marked effects. Other observers[4] found that like results came from intermittent compression of the abdominal aorta in rabbits. O. Klotz,[5] after suspension of rabbits, head downward (three minutes per day for one hundred and thirty days), noticed that a similar atheroma (yellowish calcified patches) was produced. With the manometer he showed that in rabbits in this position a great increase of pressure in the aorta is produced. Feeding adrenal tablets and gland substance by the mouth was much less apt to have any such effect.

The Fate of Epinephrine in the Organism.—The fate of epinephrine in the organism has excited much discussion. The conclusions so far arrived at have been somewhat speculative. To quote again from W. E. Dixon's[6] interesting account:

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[1] Jour. d. physiol. et d. path. gén., 1917–1918, **17**, 807.

[2] Endocrinology, 1917, **1**, 292.

[3] Comptes rend. soc. d. biol., 1903, **55**, 1374.

[4] Harvey, W. H.: Virchow's Arch. f. path. Anat., 1909, **196**, 303.

[5] Centralbl. f. allg. Path., 1908, **19**, 535.

[6] Loc. cit., p. 220.

"The introduction of adrenalin into the circulation at all times produces a very fugitive effect, and the adrenalin is destroyed. This destruction apparently goes on at the 'nerve endings' until these are saturated; for we know that after perfusing the drug through the innervated vessels only a certain amount is destroyed. What apparently happens is a combination between the adrenalin and some constituent at the periphery, which results in stimulation of the muscle, and when all this latter substance is used up the adrenalin circulates free in the blood and produces no further effect."

Von Fuerth[1] says that after even very large oral doses, or subcutaneous injections, very little is found in the urine.

Physiological Congeners of Epinephrine.—Barger and Dale[2] studied the action on blood-pressure of many amines, and found that a "sympathomimetic" effect is common to a large number of primary (fatty acid series) and secondary amines. The quaternary ammonium bases act more like nicotine. "The optimum carbon skeleton of a primary or secondary amine for the production of this type of activity appears to consist of a benzene ring with a side chain of two carbon atoms, the amino group and the benzene nucleus being attached each to a different carbon atom of this side chain."

S. Vincent[3] notes that one of the most active of the sympathomimetic amines (3 : 4 dihydroxy-phenyl-methyl-ethylamine) has been marketed under the trade name of "epinine," with the claim that it is superior to the natural product.

Evidence from Animal Experimentation.—Excisions of the medulla are inconclusive for several reasons. One is the same as mentioned in respect of the cortex—the physical impossibility of removing the medulla without damage to the cortical part. Another is the large supply of chromaffin tissue which it is practically impossible entirely to destroy, and which seems to contain efficient amounts of epinephrine.

By biological tests made on normal animals Meyer and Gottlieb[4] claimed to have shown that the adrenal veins contain more pressor substance than the general blood stream contains, thus indicating that epinephrine is certainly under normal conditions in some measure absorbed and distributed. But the work of Stewart and Rogoff[5] adds greatly to the complexity of the problem. At present no satisfactory theory of the actual action of epinephrine on the tissues in health can be formulated.

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[1] Ztschr. f. physiol. Chem., 1898, **26**, 15.

[2] Jour. Physiol., 1910–1911, **41**, 19.

[3] Loc. cit. [4] Loc. cit., p. 241. [5] Loc. cit,

Whether the chromaffin system as a whole hypertrophies after total epinephrectomy is, as far as I am informed, entirely unknown. There are few or no reliable observations on the matter. Whether epinephrine is the only active principle of the adrenal system is unknown. It is the only one so far isolated. Whether the adrenal (chromaffin) system as a whole is essential to life is unknown.

Evidence from Autopsies.—*Tumors of the Adrenal System.*—Some tumors of the adrenal medulla have been described in which there was apparently a cellular hyperplasia. In reference to their embryological derivation they have been called neurocytomata. The cells have been sometimes found to give the adrenalin reaction, and acute nephritis and high blood-pressure have sometimes accompanied them. A causal nexus has been suggested but not proved.

Chromaffin Cell Tumors.—These have also been described. They were thought to be primary in extra-adrenal chromaffin bodies. Attendant secretory phenomena were very indefinite, or not reported at all. An exact and complete morphological study of these tumors may be found in the volume of J. Ewing.[1]

C. Entire Gland.—Some authors[2] claim that the compound gland, by reason of the intimate contact of its two parts, exercises a function which cannot be duplicated by its accessory components secreting separately. This is a matter, however, which requires further experiment. The islets of Langerhans are imbedded in the pancreas, the parathyroids imbedded often, also, in the thyroid; yet the secretions of these apposed glands do not seem to be intimately connected with one another.

Our present imperfect knowledge of the whole gland physiology of the adrenals may be inferred from the following: (1) Summary of *excision experiments*, together with the (2) study of the symptoms and signs of *Addison's disease*, and (3) of the clinical phenomena attending certain *adrenal tumors*.

Excision Experiments, Whole Gland.—The first experiments in total ablation of the two glands were made by Brown-Sequard. His work extended over a number of years. He seems to have been stirred to this line of experiment by the reports just then first appearing of Addison's disease. Brown-Sequard[3] operated on dogs, cats, guinea-pigs and rabbits. His subject animals all died promptly (usually in less than twenty-four hours) after double ablation. After unilateral ablation, also, many subjects (virtually all) died. The latter accident he seems himself to have considered puzzling. He remarks of it, "With more experience I think it probable one would see some survivals." Blood of agonal subjects poisoned normal animals. Blood of normal animals (same species) temporarily revived dying subjects. In a longer *Mémoire*[1] he reviews *post mortem* lesions, considers them insufficient to account for death, and affirms that the adrenal bodies are evidently essential to the animal economy.

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[1] Neoplastic Diseases, 2d ed., Philadelphia, Saunders, 1922.

[2] Poll: Loc. cit., p. 216.

[3] Compt. rend. acad. d. sci., 1856, **43**, 422.

References to numerous later studies, conflicting and confirmatory, are assembled in Biedl's list, to which all subsequent writers, myself included, are much indebted. Biedl notes very correctly that the early confusion was due to ignorance of the exact anatomy of the accessory glands. It was especially puzzling that rats so often recovered, though it is now easily understood as due to their so often possessing accessory glands. Biedl's[2] own work was of value and significance. He devised a preparatory operation, moving the glands (with intact vessels) to the back between skin and muscle, so as to facilitate subsequent experiments. His labors have fully confirmed the general conclusion that removal of both adrenals is a fatal operation. The paper of Hultgren and Andersson[3] covers an enormous amount of anatomical and experimental ground. Strehl and Weiss[4] found that of the ordinary animals dogs lived twenty-two to one hundred and thirty-eight hours after the double operation; cats, fifteen to forty-seven hours; rats, fifteen to nineteen hours; and that after unilateral extirpation nearly all animals survived.

P. Langlois's[5] studies are also authoritative, and include a bibliography of nearly 250 names.

Phenomena after Double Ablation.—After reviewing the results of operation, and collating the anatomical facts (p. 217), one must draw at least the provisional conclusion that the adrenals are essential to life. The operative failures not due to faulty technique seem fairly attributable to accessory glands. Subject animals without extra glands die. When one gland is taken the other enlarges. When partial excision is done (Biedl) recovery will not occur unless a definite fraction of gland is left.

When the effect of the anesthetic has worn off the animal is cheerful and hungry for a few hours, or for a day or so. On the second or third day he begins to droop, refuses to eat, sits quietly in his cage, looks sick and gradually fails. The muscles become relaxed, the temperature falls and death ensues with slowly failing heart and respiration. Convulsions and fibrillary twitchings are exceptional.

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[1] Arch. gén. d. méd., 1856, **8**, 385, 572.

[2] Loc. cit.

[3] Skandinav. Arch. f. Phys., 1899, **9**, 73, with over 200 references.

[4] Pflüger's Arch., 1901, **86**, 107.

[5] Fonctions des capsules surrénales, Richet's Trav. d. lab. d. phys., 1898, **4**, 1; 1902, **5**, 21.

If we presume, as seems to be necessary, that death is due to absence of more than one secretory element, the analysis of the condition is specially difficult. Often death comes so quickly that time for study of symptoms is unavailable. The fall of temperature has been noted again and again. The postoperative fall, common after a variety of operations, is recovered from. When the other symptoms of adrenalectomy begin to appear there is a progressive drop in the rectal temperature, which just before death may even reach 30° C. The rapid emaciation is partly due to starvation. The muscular relaxation and nervous apathy are unexplained. A few studies in metabolism have been made—too few to be of decisive value. Polyuria has been described in some animals. Compensatory hypertrophy of interrenal tissue can be easily demonstrated (Biedl[1]) in step operations, giving time for such an effect to occur. Upon the chromaffin system the effects of total double excision are uncertain.

The appearance of *pigmentation* after double ablation has been laboriously studied by numerous authors, with questionable results. References to the largely controversial literature may be found in Biedl's list. Biedl himself positively affirms that by the experiments of himself and Hofstaetter a definite influence of the entire gland upon pigment metabolism has been proved. He believes that the cortex is probably the part mainly, or perhaps exclusively, concerned, his experiments on the medulla being insufficient to justify sweeping conclusions.

The effect of double adrenal excision on the other glands of internal secretion is extremely obscure. The literature is controversial.

Clinical Data.—Information as to the functions of the whole gland is considerably enlarged by the clinical and *post mortem* studies of acute total hypoadrenia and of Addison's disease. (The appropriate sections of this book may be consulted for details.) Addison's disease is probably best viewed as a chronic total hypoadrenia. There have been some reported cases of Addison's disease in which the adrenals were found "unaltered" at autopsy. Possibly one is justified in bringing in here the explanation offered for the rare cases of acromegaly in which the pituitary was "negative," namely, that a "functional" or chemical fault of secretion may exist without discoverable microscopical changes.

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[1] Loc. cit.

Tumors of the Whole Gland.—When a destructive tumor affects only one gland hypoadrenia is absent. When a destructive tumor affects both adrenals, Addison's disease has been known to develop. Concurrent hyperplasias of the cortex and of the medulla in the same person have never been observed, so far as I am acquainted with the literature. The several effects of hyperplasia of either part have been mentioned in other sections.

DISEASES OF THE ADRENALS.

DEVELOPMENTAL ANOMALIES.

Congenital Absence.—Congenital absence of the glands (autopsy in adult years) has been claimed or inferred so rarely that one would be justified in thinking that either they were overlooked or that some accessory gland replaced them. *Congenital hypoplasia* of one or both glands, or of cortex or medulla of one or both glands, has been noted mainly in monsters (Biedl), and has no special endocrine significance. "Primary" atrophy so-called is probably an acquired condition due to syphilis, tuberculosis or pressure of tumors.

CIRCULATORY DISTURBANCES.

General passive congestion produces a moderate fibrosis. Acute congestion of the glands (especially of the medulla) is common in all acute infectious diseases. In autopsies after death from any disease whatever hemorrhages, organized or fresh, are found in 5 to 10 per cent of the cases.

INFLAMMATIONS OF THE ADRENALS.

Among the acute inflammations are secondary suppurative processes due to extension of local abscesses or to infection by way of the blood. Syphilis of the adrenals is not often a separate clinical entity.

Tuberculosis.—Tuberculosis of the adrenals is the most important of the chronic inflammations. The adrenals are very prone to tubercular infection. Caseation, softening and "cold abscesses" are not uncommon in connection with general tuberculous processes, and primary tuberculosis of the adrenals is also met with. Either process may vary in degree from the early deposit of a few tubercles to a virtually complete destruction of one or both glands. When both are extensively involved, and there are no accessory glands to supply the deficiency, Addison's disease seems to be the invariable consequence.

Degenerations.—Among the degenerations amyloid and calcium deposits are the commonest forms of trouble. Neither appears to be entirely destructive of the function of the gland.

CYSTS OF THE ADRENALS.

Cysts of the adrenals are also observed. The writer once saw at autopsy a left-sided cyst nearly 12 cm. in diameter. The thickened cyst-wall still contained a considerable amount of cortical tissue. Bilateral congenital cysts have been reported as the apparent cause of Addison's disease in early infancy.

CELLULAR TUMORS OF THE ADRENALS.

Cellular tumors of the adrenals constitute a large and difficult chapter in pathology. Destructive tumors tend to abrogate, while hyperplasias and adenomata are supposed to increase the secretory activity of the part of the gland involved. These questions are touched on in the Sections on Physiology and on Secretory Diseases.

Structural details are to be found in the text-books of surgical pathology. J. Ewing[1] describes hyperplasia of the cortex, both nodular and diffuse (*struma adrenalis* of Virchow), as well as adenoma and carcinoma. He notes in the medulla the not infrequent occurrence of hyperplasia, which may be of glia tissue, or chromaffin tissue, or both.

Primary tumors of the chromaffin bodies (extra-adrenal) have already been mentioned (p. 225). Primary tumors of aberrant cortical rests are a debatable ground. Ellis[2] affirms, against their adrenal origin, that no hypernephromata have been observed to cause the anomalous sex marks noted with true cortical adrenal hyperplasias. Discussion and literature may be found in Ewing's volume.

[1] Loc. cit., p. 225.

[2] Quoted by Ewing (Loc. cit.).

SECRETORY DISEASES.

The secretion of each portion of the gland may theoretically be *increased, diminished, absent* or *depraved;* but our knowledge is very limited.

INCREASED SECRETION (CORTEX ONLY).

It has been occasionally noted in women and girls that cortical hyperplasias (not the small multiple nodules, or minute adenomata often seen at autopsy,[1] but diffuse cellular growths of some size) are associated with the development of male attributes—face-hair, a bass voice, marked hypertrophy of the clitoris and virile mental qualities. This is commonly called *virilism,* or *feminine pseudohermaphroditism.* A causal relation is presumed but not proved. Such tumors occurring in adult men are clinically negative, perhaps only reënforcing the male gonad. In boys there is some questionable evidence that adrenal hyperplasias induce a precocious puberty, not a male pseudohermaphroditism. The question has been recently considered by Jump, Beates and Babcock,[2] who reported an interesting case, and reviewed the literature.

Krabbe's interpretation of the phenomena, namely, that the "adrenal" hyperplasia is really a tumor from an embryonic testis rest, is mentioned and commented upon on page 289.

Of other possible clinical effects of cortico-adrenal hypersecretion there is at present no knowledge.

INCREASED SECRETION (MEDULLA ONLY).

Many efforts have been made to connect high blood-pressure and degenerative arterial diseases in a causal way with the known toxic effects of prolonged epinephrine injections in laboratory animals (p. 223). In some medullary hyperplasias found at autopsy such an inference is backed at least by the concurrence of the two phenomena; but the chances of error are myriad. The question is entirely undecided.

That experimental injections of epinephrine produce or aggravate many of the symptoms of Graves's disease has been commented upon on page 91. But proof is lacking that the adrenal medulla is causally related to this disease.

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[1] Krabbe: Loc. cit., p. 206.

[2] Am. Jour. Med. Sci., 1914, **147**, 568.

DECREASED SECRETION (CORTEX ONLY).

Of uncomplicated cortical hypoadrenia there are no clinical symptom-complexes, except in so far as the pigmentation of Addison's disease is referable to cortical deficiency (pp. 227 and 236). The unreliability of this sign taken alone is noted elsewhere.

DECREASED SECRETION (MEDULLA ONLY). HYPOADRENIA MEDULLARIS. "INSUFFISANCE SURRÉNALE."

Our actual knowledge is quite insufficient to identify this supposed disorder as a clinical secretory entity. The conception seems to have started in France with É. Sergent and his persevering studies of the "white line." Since the beginning of the century Émile Sergent has from time to time published papers on the appearance of a white line (*ligne blanche surrénale de Sergent*) which follows linear stroking of the skin of the abdomen when the adrenals are diseased (medullary parts?) and blood-pressure is low. These papers were finally collected in a volume.[1] Sergent's own description is as follows: "Like the meningitic line, the adrenal line is to be sought on the skin of the abdomen—not because it cannot, like the physiological white line (a white line with a red border), be found on the back of the hand, but because the physiological white line is harder to produce on the belly. Not the least compression is necessary; it is enough to run the ball of the finger (not the nail) or any soft blunt object rapidly and lightly over the skin. A triangle, rectangle or other geometrical figure is usually traced, preferably around the navel. The line does not appear at once, but in from thirty to sixty seconds. It lasts from two to five minutes. It is, of course, wider than the object used in stroking the skin. It never has a pink zone on either side, in this regard being distinguished from the physiological white line." It is more marked, he says elsewhere, the lower the pressure, and is virtually pathognomonic of adrenal insufficiency.

A large literature has accumulated on the subject of the white line. Many careful students say it is a casual vasomotor phenomenon of no special clinical importance, and often not seen even when the blood-pressure is low. How to discriminate low blood-pressure in other diseases from low blood-pressure in adrenal disease Sergent has not told us, unless he means that all low blood-pressures are of adrenal origin.

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[1] Études cliniques sur l'insuffisance surrénale, 1898-1920, 2d ed., Paris, Maloine et Fils, 1920.

It is true that at autopsy after many acute febrile infections the adrenal marrow is found soft and bloody, but *post mortem* changes must be allowed for; the chrome reaction is always abolished within twelve hours after death. The carefully conducted experiments of Stewart and Rogoff[1] show that laboratory animals with cut adrenal nerves, and biologically no discoverable trace of epinephrine in the blood, can live indefinitely in health and comfort. Even when acute hemorrhages into the medulla occur one does not know but that the accessory chromaffin bodies are entirely able to supply the hypothetical lack of epinephrine in the body. They give the chrome reaction; they contain epinephrine. The present writer does not wish to say that such a disorder is impossible—only that its existence is entirely unproved.

For the other clinical signs, the diagnosis and the treatment, the extensive French and Italian literature may be consulted. There is also a large American following. The most enthusiastic support for the existence of the disorder is to be found in commercial circulars of manufacturers who have "adrenal gland" to sell. They do not even say whether it is cortex or marrow, nor recognize the fact that adrenal medulla ought to be given only by hypodermic. (For therapeutic details later sections may be referred to.)

When, in addition to his white line, the patient happens to have a pigment patch on his body anywhere—freckles, sunburn, congenital birth marks, stains of old skin diseases (anything will serve)—the disease becomes dignified with the name "Addisonism," and the cortex is presumed to be also deficient.

TOXIC SECRETION. INVERTED SECRETION.

Toxic chemical deviations of the secretion of the whole gland, or of either part ("toxic adrenalism"), and combinations involving a total hyperadrenia, or a plus or minus cortical with a minus or plus medullary secretion, respectively, have not been identified at the bedside.

DECREASED SECRETION OF THE ENTIRE GLAND.

Acute Hypoadrenalism (*Hypoadrenia Totalis Acuta*).—This condition was noticed and described by Virchow[2] a long while ago. The patient is suddenly seized with pains in the abdomen and the picture of acute peritonitis is presented, with collapse, convulsions, coma and rapid dissolution. Autopsy has shown destruc-

[1] Loc. cit., p. 222.

[2] Biedl: Loc. cit.

tive hemorrhages of the two adrenals, attributable to trauma, thrombosis or embolism. Sometimes suppurative processes have been found. Vallois and Roume[1] have recently reported lesions of the adrenals in a case of sudden death of a new-born infant.

The condition is comparable to the rapid exitus of laboratory animals after double excision of the adrenals.

Chronic Hypoadrenalism. Addison's Disease.—Name and History.—This disease is still known in all languages by the name of the English physician, Thomas Addison, whose first accounts date from before the Crimean War. He spoke before the South London Medical Society[2] with hesitancy of his observations, and, indeed, he seems to have believed at that time that the severe anemia his first patients showed was the principal symptom. "In three cases only was there an inspection after death, and in all of them was found a diseased condition of the suprarenal capsules. . . . Was it possible for all this to be merely coincidental? . . . . Making every allowance for the bias and prejudice inseparable from the hope or vanity of an original discovery, he confessed that he felt it very difficult to be persuaded that it was so."

Some years later he had fully made up his mind as to the character and symptoms of the new disease, and in a thin quarto volume,[3] with handsome and well-executed full-page colored plates of the cutaneous (Figs. 42 and 43) and visceral signs, he presented to the profession virtually a complete account. He reported 11 cases. The anemia which he emphasized has not seemed to later students so marked a sign, but to his description in other regards but little has been added. After much discussion physicians to-day also generally subscribe[4] to Addison's view of the pathogeny of the disease, namely, that it is due to a secretory deficiency of the entire substance of the adrenal glands.

Etiology and Pathological Anatomy.—The only essential organic condition at autopsy is a slowly developing destructive lesion of both adrenals. The lesion is generally an advanced tuberculosis, with caseation, softening, calcification and fibrosis. It may be primary; it has been associated with or seen to follow caries of the spine, lymph node tuberculosis and phthisis. In order to produce the symptom-complex both glands must be affected, and there must be no supernumerary glands large enough to meet the chemical emergency. Fibrosis from other forms of chronic inflammation (syphilis) and atrophy from the pressure of tumors in or near the glands are conceivable additional causes, but they are rare. Congenital cystic glands have been found at autopsy. Circulatory derangements also occur.

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[1] Bull. Soc. d'obst. et de gynéc., 1923, **12**, 82.

[2] Loc. cit., p. 209.

[3] Loc. cit.

[4] Biedl: Loc. cit.

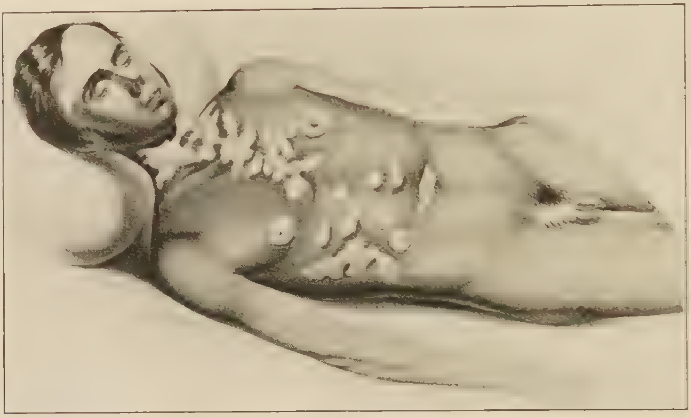

Fig. 42.—Addison's disease. Mr. S., exhibiting peculiar discolorations and white patches of integument. (Photograph from Thomas Addison's original colored lithograph.)

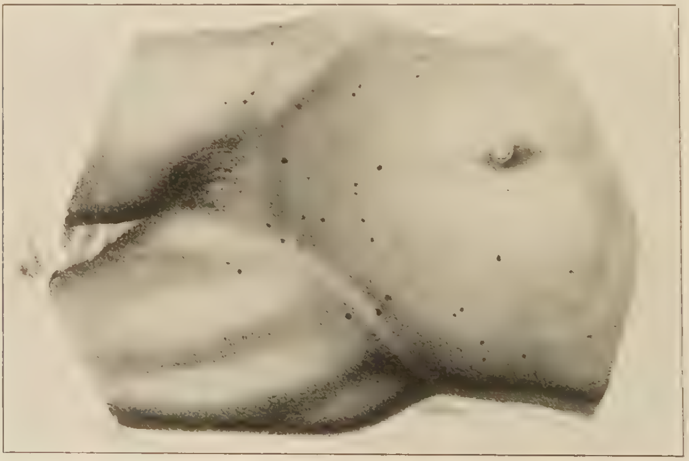

Fig. 43.—Addison's disease. Elizabeth L. Abdomen, exhibiting general dinginess of integument, with several small circumscribed deposits of darker pigment. (Photograph from Thomas Addison's original colored lithograph.)

There are a few cases in the literature said to be correctly diagnosed in which the adrenals were found intact. One may, perhaps, be allowed to suppose in such cases that there were functional disturbances of the glands not shown by microscopical methods. In some of them, however, the solar plexus had been subjected to pressure, with atrophy or softening as a result. This latter condition has led to the claim by certain authors that Addison's disease is primarily a disease of the abdominal sympathetic and only secondarily of the adrenals. A larger amount of pathological material studied by modern methods may clear up these divergences. Present explanations are speculative.

Frequency.—The disease is extremely rare. By reason of its rarity many hundreds of cases have been reported. How many more have been observed is, of course, conjectural. The diagnosis is not always easy and statistics of cases not coming to autopsy are questionable. Of the clinical "cases" that I have seen shown at medical societies in New York fully one-half were of doubtful diagnosis. A physician in active hospital and private practice may see 10 or 15 cases in a lifetime. L. G. Rowntree[1] notes that 47 cases of Addison's disease seen at the Mayo Clinic since 1912 represent about 1 to every 6600 patients registered during the same period.

Age and Sex.—The disease is much more frequent in males. The proportion ranges around 2 to 1 in various series of reported cases. The condition is commonest between the twentieth and fortieth year, but no age is exempt. Osler mentions (no reference) a congenital case. The baby lived eight weeks. The color of the skin was yellowish-gray. At autopsy large cystic adrenals were found.

Symptoms.—The *onset*, as a rule, is rather insidious. Besides tuberculosis, influenza is thought by some to be the commonest antecedent. The severe anemia which Addison noted is not always present. More frequent and prominent symptoms are the general languor, the flabbiness of the muscles, emaciation of the tissues, remarkable feebleness of the action of the heart, the low blood-pressure, the irritability of the stomach and "the peculiar change in the color of the skin" (Addison). In course of time the weakness increases, intractable diarrhea sets in and coma or convulsions mark the end of the patient's suffering. Death is sometimes sudden.

The pathogenesis of these symptoms is obscure. As regards the muscular flabbiness, one immediately thinks of the recent researches of Royle and Hunter[2] in the matter of the effect of the sympathetic on muscular tonus. The sympathetic is also the accelerator of the heart, and presumably has something to do with the vascular tension, though the details of the physiology are very ill understood. Unfortunately there are very few exact modern accounts of the pulse-rate and blood-pressure in these patients. Rowntree[1] noted pulse-rates from 75 to 100 and systolic blood-pressures from 60 to 154. Lower figures have been reported.

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[1] Jour. Am. Med. Assn., 1925, **84**, 327.

[2] Loc. cit., p. 31.

In respect of the pathogeny, the most puzzling symptom of all is the *pigmentation of the skin* (Figs. 42 and 43). A separate volume would not hold a review of the literature of the origin and chemistry of Addisonian pigmentation. For details the large works must be consulted. Some brief comment will be found under Physiology (p. 227).

Clinically, too, the matter of pigmentation is not without its difficulties. There are many chronic skin diseases without known adrenal derangement in which the pigment layer of the skin is affected. Chronic uterine disease is sometimes associated with patches of brownish discoloration. In pregnant women (particularly brunettes) there is a darkening of the skin in general and a heavier deposit of pigment around the nipples and genitals. In exophthalmic goitre one sometimes sees rather marked pigmentation of the skin. Localized patches of pigment come and go (freckles, sunburn, nævi) on many otherwise healthy skins. In some melanotic tumors the skin is much darkened. Then there is racial coloring to be considered (negro, mulatto, Indian), and the chronic poisoning from silver (argyriasis), and the bronzing in some cases of diabetes. Peritoneal tuberculosis, without involving the adrenals, may cause pigmentation (Osler). Finally, uncleanliness and the chronic scratching due to pediculosis will make a discoloration in the vagabond which may deceive even an experienced observer.

The cutaneous discoloration in Addison's disease has, however, some characteristic features. It is, as a rule, diffuse, though perhaps more marked on the parts of the body usually exposed to light and air. The color is apt to be brownish-black. It often affects the mucous membranes of the lips and fauces as well as the skin. The serous membranes at autopsy may show the same color diffusely or in patches. Addison remarked that the patient looks rather like a mulatto. Rowntree notes that one of his patients, an engine driver, was "like a negro." Sometimes irregular black spots $\frac{1}{2}$ inch or less in diameter may be scattered over a brown skin. Sometimes there are large patches of *pigment atrophy*, producing the appearance of vitiligo. Finally, cases have been described in which the pigment was not characteristic, or was entirely absent. Possibly these are instances where the local destructive process has affected the cortex less than the marrow. On another page it has been noted that with successful organotherapy the pigmentation may become less noticeable.

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[1] Loc. cit.

The white line of Sergent may be present. Its significance has been discussed on another page.

Shock and Pain.—Various writers have noted the shock-like attacks which patients have suffered in the later stages of the disease. Pain in the belly may be due to the constant gastro-intestinal disorders or to the adrenal lesion. Angina pains were described by A. L. Muirhead,[1] whose account is a brave contribution to autopathography.

Laboratory studies have been made by Rowntree. They showed a basal metabolic rate within normal limits in a majority of the cases. Epinephrine injections temporarily increased the rate. Acidosis was noted in a few instances. Blood volumes were generally normal. Electrocardiograms were negative.

Rowntree noticed in a few instances the slow, irregular, sighing respiration described long ago by C. Biot[2] as associated with intracranial lesions.

There are not many data on urinary analyses. They are for the most part negative.

Other symptoms are casual. Tuberculosis of the lungs, spine, lymph nodes or joints may precede the development of Addison's disease. Tumors primary in the adrenals may possibly cause symptoms of pressure locally or of metastatic invasion elsewhere. Of the rare cases of luetic infection it is not necessary to speak more particularly.

Diagnosis.—The reader who has gone attentively over the account just given will perceive that the diagnosis may be easy, and may be difficult or impossible. Nondescript forms of pigmentation only add to the perplexity of the student, and pigmentation is sometimes absent. Low blood-pressure is found in the late stages of all forms of chronic tuberculosis. Probably the muscular asthenia and flabbiness, with the concurrence of an obstinate gastritis (without roentgen-ray indications of cancer or ulcer) is the most suggestive early sign. It is probable that many cases have come to autopsy without a diagnosis—an event partly attributable to the confusing character of the signs and partly to the rarity of the disease.

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[1] Jour. Am. Med. Assn., 1921, **76**, 652.

[2] Lyon méd., 1876, **23**, 517.

Duration and Prognosis.—The disease is sometimes rapidly fatal. Subacute hypoadrenia totalis has been reported in which nevertheless the skin pigment appeared promptly. Biedl[1] quotes from Straub the history of a case which survived only seventeen days. At autopsy there was found thrombosis of both adrenal veins. It has been mentioned that death is sometimes sudden. On the other hand, some cases live for years. Remissions and even apparent cures have been occasionally observed.

Treatment.—The therapeutic details of adrenal administration are given in the next section. The methods of preparation of adrenal extract, both cortex and medulla, have been much improved of recent years, and recent results of adrenal treatment in Addison's disease are far more encouraging than formerly.

Symptomatically much may be done by confining the patient to bed and guarding against exertion. When anemia is present the usual remedies for anemia must be given. Strychnine is also indicated. For the diarrhea large doses of bismuth are helpful. A rigid adaptation of the diet to the state of the patient's stomach is, of course, desirable. An exclusive milk diet will agree with many patients better than anything else.

Complicating conditions can only be dealt with on general principles. The patient's friends should be warned of the gravity of his condition.

ADRENAL THERAPEUTICS. DOSAGE AND ADMINISTRATION.

Sources of Material.—Bullocks' glands are commonly used. For comments on the use of the glands of castrated animals, as also in reference to the undesirability of freezing and cold storage, Chapter IV may be consulted.

Preparations.—*Dried Whole Gland, Cortex and Medulla.*—After the fat is removed the cortex of the adrenal can be readily distinguished from the medulla by its lighter color and can be trimmed off with a sharp knife or scissors. By using sufficient care the two parts can be perfectly separated for all practical clinical purposes. The gland material should be rapidly dried in the cold, and pulverized. Treatment with fat solvents is to be avoided. For cortex no method of standardization is now available except weighing. The dose is experimental, usually 1 to 5 gr. E. J. Baumann[2] has recently analyzed three commercial adrenal cortex preparations, and found them to contain very appreciable amounts of epinephrine. He believes that the vomiting and nausea so often caused by so-called cortex preparations is due to their epinephrine content.

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[1] Loc. cit.

[2] Endocrinology, 1923, **7**, 81.

Dried cortex and *dried medulla* are not official, but the United States Pharmacopœia (9th edition, 1916), in the usual barbarous Latin, listed dried whole gland as "*Suprarenalum Siccum*, Dried Suprarenals," and defined the preparation as "Suprarenal glands of animals used for food by man, cleaned, dried, freed from fat and powdered, and containing not less than 0.04 nor more than 0.06 per cent of epinephrine, the active principle of the gland (lævo-methyl-amino-ethanol-catechol)." A moisture of 7 per cent was allowed; ash should not exceed 7 per cent. Assay was to be made by comparing the manganese dioxide color reaction of the substance to be tested with a standard color. The dose was given as 4 gr. (0.259 gm.).

This quotation well illustrates the general misinformation in the profession on the subject of the adrenal gland. The above prescribed process standardizes the medullary fraction; it ignores the cortical. It is pleasing to note that the Tenth Decennial Revision (1926) omits "Suprarenalum Siccum" altogether.

Dried medulla may be standardized in the same way (and much more rationally), and may be given by mouth in the same dose as whole gland, but gastro-intestinal irritation is common, absorption is imperfect and uncertain, and such medication is not, I believe, advised except in commercial circulars. The active principle is given hypodermically instead.

Extracts. Many chemical studies of the lipoids of cortex and medulla have been made,[1] but nothing is definitely known of their therapeutic action. Some New York clinicians, by preference, separate the nucleoproteids of the entire gland from the "residue" containing the globulins and albumins, and allege that entirely different clinical effects may be got from the two. No active principle of the cortex is known.

Epinephrine, the active principle of the medulla, or one of its active principles, has been already extensively discussed. It is official in the Tenth Revision of the United States Pharmacopœia. The hypodermic dose is given as $\frac{1}{120}$ grain. The official latin name is *Epinephrina.*

Epinephrine is a subject of great clinical importance. It has a variety of trade names, as "suprarenin," "l-suprarenin," "adrenalin," "paranephrin," "epirenan," "paraganglin," "myosthenin," "sphygmogenin" and others. By the current British Pharmacopœia it is recognized as *Adrenalinum*, and the 1 to 1000 aqueous solution of the chloride is also listed.

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[1] Biedl: Loc. cit.

In practice everywhere epinephrine is dispensed as chloride, in 1 to 1000 aqueous solution, with a trace of antiseptic added. It may be given by mouth in doses of 5 to 10 minims (0.5 cc.) or somewhat more; but, as has been said, it is unreliable and uncertain when so given, and is apt to cause nausea. Trias and Dorlencourt[1] recommend oral administration in concentrated form, first making the dose isotonic with Ringer's solution. It may also be administered in a saline enema. The common and effective method is by hypodermic (5 to 10 minims, or $\frac{1}{4}$ to $\frac{1}{2}$ cc.).

Therapeutic Uses of Adrenal Preparations.—Adrenal medication is, of course, specifically indicated in those diseases in which the patient's own gland is either in whole or in part insufficient.

The classic example of total hypoadrenia is *Addison's disease*. The history of adrenal therapy in this disease goes back many years before the discovery of epinephrine. The crude methods of preparation and the irregular dosage of former days were followed by a few uncertain successes and many disconcerting failures. The story may be found in any of the older text-books of medicine. Latterly the hypodermic administration of epinephrine coupled with suitable oral doses of properly made whole gland or cortex only has in many instances proved to be of considerable benefit. Rowntree[2] recommends dry whole gland by mouth in doses adjusted to the patient's tolerance, and hypodermic doses of epinephrine three times a day, with one daily rectal injection of epinephrine. He very properly notes that the individual patient must be studied, and gastric irritation avoided by every possible means. Sometimes the oral dose is better tolerated on a full stomach. Sometimes cortex only worked more satisfactorily. He reports that when the stomach is equal to the task a good proportion of cases recently cared for did well on this treatment, and the pigmentation also faded as the general condition improved.

The same disadvantage attends substitutive therapy in adrenal deficiency as in other endocrine troubles—the greater the lack, the harder to supply it by artificial means.

Other total adrenal deficiencies of a temporary or "functional" kind are more problematic in their occurrence, but if the diagnosis can be made adrenal therapy is indicated.

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[1] Compt. rend. soc. de biol., 1922, **87**, 1189.

[2] Loc. cit.

In *hypoadrenia medullaris*, when a diagnosis can be positively arrived at, epinephrine is a rational remedy. Even in cases where the diagnosis is in doubt some temporary benefit possibly arises from the elevation of blood-pressure it tends to produce. It should be given by hypodermic, and the dose repeated cautiously from time to time, as occasion may require; the action of a single dose is very evanescent.

S. Shapiro and D. Marine[1] noted great gain in weight and in strength in a case of *exophthalmic goitre* by giving fresh adrenal cortex. Commercial dried gland failed to have the same effect. Marine[2] reaffirms this fact from larger experience. (See also Marine and Baumann, loc. cit., p. 222.)

Miscellaneous Symptomatic Clinical Uses of Epinephrine.—The symptomatic uses of epinephrine in surgical and medical practice are well known, and need be only summarized. They follow directly upon its physiological properties.

The effect of epinephrine upon the acutely failing heart of shock, of diphtheria and other bacterial intoxications, of chloroform and ether anesthesia, is sometimes life-saving. The drug must be given in full doses and promptly by intravenous injection. After severe acute hemorrhages epinephrine may be added in proper doses to saline infusions. For chronic low blood-pressure of any origin epinephrine may be used for its pressor effect, but its action is very temporary.

In many cases of *spasmodic bronchial asthma* epinephrine is of value. The *rationale* of its action seems to lie in its effects upon the swollen mucosa of the bronchioles.

As a *local hemostatic* in surgical operations of many kinds epinephrine is of great value. Combined with cocaine, eucaine and novocaine it seems physiologically to reënforce the anesthetic effect of these drugs,[3] as well as diminish the bleeding from the surfaces. In operations about the mouth, nose, pharynx, eye, bladder, and even in spinal anesthesia, in combination with one of the drugs mentioned, epinephrine is in very general use.

Barr[4] recommended injections of epinephrine into serous cavities just emptied of effusion, claiming that reaccumulation was less apt to occur. In inaccessible internal hemorrhages epinephrine used to be given. It has, I believe, been replaced largely or entirely by the safer and more efficient remedy, thromboplastin.

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[1] Endocrinology, 1921, **5**, 690.

[2] Therapeusis of Internal Diseases, Forcheimer-Blumer edition, New York, Appleton, 1924.

[3] Meyer and Gottlieb: Experimentelle Pharmocologie, 6th ed., Berlin, 1922.

[4] Brit. Med. Jour., November 21, 1903.

Contraindications for Adrenal Preparations.—The cardinal contraindication for *epinephrine* is high blood-pressure, whether arising from chronic cardiac or renal disease, or from primary disease of the arteries. Epinephrine is contraindicated in Graves's disease and all forms of hyperthyroidism; even a single small dose may greatly aggravate the symptoms, especially when the blood-pressure is high. This fact is the basis of the Goetsch test for hyperthyroidism. Occasionally personal idiosyncrasies for epinephrine also are met with, and, considering the readiness with which laboratory animals sometimes die after doses only a little bit too large, the clinician should exercise every care when giving epinephrine to new patients not to overstep the initial limits of safe dosage.

It is a fortunate fact that with the doses used ordinarily for therapeutic purposes in the human subject glycosuria is a very rare accident. But on general principles the use of adrenal medulla should be avoided in patients with diabetes, except as an antidote for the hypoglycemia following dangerously large doses of insulin. Further details of this accident are to be found in the next chapter.

When certain preparations of *whole gland* have been given for some time by mouth I have noticed a remarkable stiffness of the pupil for light, and the knee phenomenon may disappear. These effects are not alarming unless a physician acquainted with the implications himself be the patient; but when they appear the dose should be reduced or the remedy laid aside for awhile.

CHAPTER VIII.

INTERNAL SECRETION OF THE PANCREAS.

Terms.—The pancreas has a quaint Greek etymology, πᾶν, all, and κρέας, flesh. The pancreas is thus called in all the "culture languages" of Europe. In English it is also occasionally called the "abdominal sweetbread" to distinguish it from the thymus, which is the ordinary sweetbread of the meat shops. At the abattoirs the butchers know it as "whitebread."

ANATOMY OF THE PANCREAS.

The *gross anatomy* and the *relations* of the pancreas are familiar subjects, fully treated in the text-books. The gland has a compound racemose structure like the salivary glands. It is about 18 cm. long, 3 to 4 cm. wide at the right extremity and over 1 cm. thick at the upper border. The right end is thickened into a *head*, and the *body* tapers thence into a *tail*, which is in relation with the spleen, and lies above the left kidney and adrenal body. The pancreas weighs from 60 to 110 gm.

As to position, it lies transversely across the abdomen behind the stomach and is separated from the first lumbar vertebra by a number of vital structures, among them the vena portæ, the inferior mesenteric vein, the superior mesenteric artery and vein, the vena cava and the aorta.

The head is embraced by the concavity of the duodenum. Through head and body runs the main pancreatic duct, *canal of Wirsung*, which unites ordinarily with the common bile duct, and opens into the duodenum by a slightly raised orifice called the *papilla of Vater*. Sometimes the two ducts fail to unite and open separately into the duodenum.

The main *vessels* are the splenic artery and the pancreatico-duodenal twigs of the hepatic and superior mesenteric arteries.

The *nervous supply* is from the sympathetic and parasympathetic systems.

Histology.—The pancreas appears to consist of two separate structures, the one closely interwoven with the other. A system of racemose gland cells secretes externally by way of the canal of Wirsung into the bowel; a system of islets or islands, called the *islands of Langerhans,* are believed to be the seat of the internal

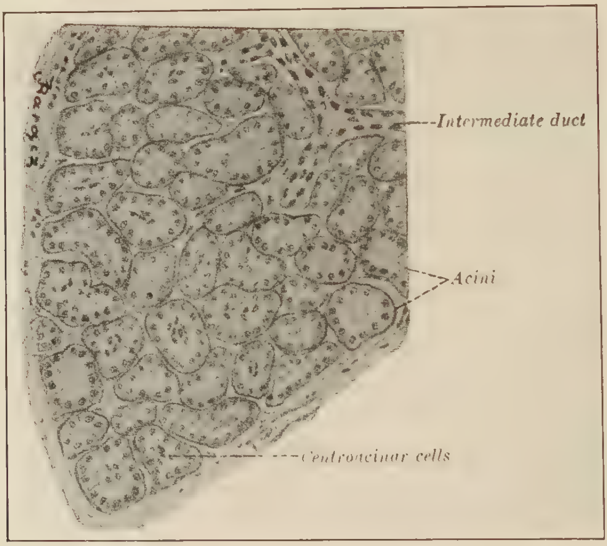

FIG. 44.—Section of a dog's pancreas. × 175. (Szymonowicz.)

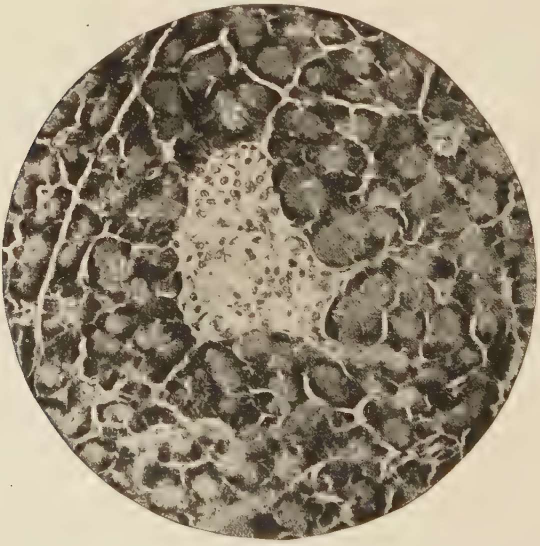

FIG. 45.—An islet of Langerhans in pancreas of dog. × 300. (Sharpey Schaefer.)

secretion. Reference to the adjacent figures will show the cellular details of each system (Figs. 44 and 45).

It is by no means proved that the islets produce the internal secretion of the pancreas. But this is the more general view. Many cases of diabetes at autopsy have shown sclerosis of the islets as the pronounced lesion. The impression is perpetuated in the name given to the newly discovered internal secretion, *insulin*. Yet there are cases of diabetes seen at autopsy every now and again where the microscopical appearances are negative. Allen's view is noted on page 251.

Development.—The pancreas appears in the embryo before the second month. The ducts arise from the infolded epithelium of the primitive gut (hypoblast). The connective tissue and vessels are of mesoblastic origin. The parenchyma and islets are derived from the ducts.

PHYSIOLOGY OF THE PANCREAS.

The pancreas is a gland with both an *internal* and an *external secretion*.

External Secretion.—The external secretion is discharged into the duodenum, and is a pale yellow alkaline juice containing multiple ferments; a proteolytic ferment, *trypsin;* a starch-converting ferment, *amylopsin;* a fat-splitting ferment, *steapsin;* a milk-curdling ferment, *pancreatic rennin*. So many are known; there may be more. These ferments are of capital importance in the intestinal digestion of food, and they appear to activate and to be activated by the bile from the liver. The study of them, however, is apart from the object of this book, except in so far as they are related to the intestinal hormone *secretin*, which is referred to in another chapter.

Internal Secretion.—*Historical.*—For many years it was supposed that the pancreas had no function except external secretion. Clinicians of the later part of the last century who followed their fatal cases of diabetes to the *post mortem* room frequently noted destructive changes in the pancreas, but excision experiments of that day in animals were negative, even in the hands of so ingenious and gifted an experimenter as Claude Barnard.

It was not until 1889 that Minkowski and Mering,[1] in Germany, and de Dominicis, in Italy, succeeded in removing enough of the pancreas in dogs to produce a glycosuria, well marked, persistent and accompanied by many of the other symptoms of human diabetes. Sandmeyer[1] a few years later found that by removing a suitable portion of the pancreas a mild and stationary or slowly progressing glycosuria could be produced—a condition which gave invaluable opportunity for experimental study. Publications of immense volume and comprehensiveness followed in the next decade. Lombroso's monograph[2] is nearly a complete story of this work up to the date given. References are full. It was shown, as a brief summary of these studies, that by proper diet and by graduation of the operative technique, experimental pancreatic diabetes can be made to exhibit nearly all the faults of carbohydrate, protein and fatty metabolism noticed in the disease in man.

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[1] Arch. f. exper. Path. u. Pharmakol., 1893, **31**, 85.

J. J. R. Macleod[3] summarized the problem of that date as follows: "There are in general two questions to be considered: First, why pancreatectomy disturbs carbohydrate metabolism; and secondly, whether this disturbance involves the glycogenic or glycolytic mechanism. . . . Several possibilities exist: (1) That the external secretion, that is, the secretion into the intestine, is essential for the proper digestion and assimilation of carbohydrate; (2) that the extirpation of the pancreas seriously damages the underlying nerves and sets up a constant irritation of the hepatic branches, and therefore a constant production of dextrose by the liver; (3) that the gland has the power of neutralizing or destroying certain toxic substances in the blood while this is circulating through it, and that these toxic substances interfere with the glycogenic or glycolytic functions; (4) that the gland produces an internal secretion . . . which exercises 'hormone' control over the glycogenic or glycolytic functions, or which destroys toxic substances that would otherwise affect these processes."

To dispose of the first two possibilities the well-known experiments of Minkowski and Hédon are enough. They have been repeatedly verified. The entire pancreas in the dog is removed except the processus uncinatus, which is grafted into the belly wall with artery and vein attached. The main pancreatic duct is tied off. The animal suffers from pancreatic indigestion, passes fatty stools and grows thinner and weaker, but no glycosuria results. When the graft has grown into its new place, and collateral circulation has become established (provision being made, if necessary, by a hole in the belly wall, for the outward escape of the external secretion, which would otherwise become encysted), the original vessel and nerve connection is severed. Still no glycosuria results. Finally the entire graft is removed. Severe glycosuria at once appears, and the animal dies in a few days. These facts exclude nervous influences and point strongly to the existence of an internal secretion.

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[1] Ztschr. f. Biol., 1895, **31**, 12.

[2] Ergebn. d. Physiol., 1910, **9**, 1.

[3] Diabetes: Its Pathological Physiology, London, Arnold, 1913, p. 88.

For years the efforts of students of the highest training and ability were concentrated upon the problem of isolating this supposed internal secretion. The literature is enormous. It has now for the most part only a historic value, and need not be summarized. Cohnheim, in 1903, announced that he had identified the internal secretion of the pancreas as a co-ferment working with muscular ferments to metabolize glucose. Later observations seemed to show that bacteria were responsible for his results. In Graham Lusk's laboratory Murlin and co-workers,[1] after a long series of fruitless experiments, rather pessimistically affirmed that the pancreas perhaps has an internal secretion, which owes its efficiency merely to its modification of the alkalinity of the blood in some way.

It remained for F. G. Banting, working in Professor MacLeod's laboratory at the University of Toronto, with the assistance of C. H. Best, to make the fortunate discovery that there is an internal secretion of the pancreas, that it apparently is non-protein in structure, that it is destroyed in the stomach and bowel, that it may be given with perfect success by hypodermic and that proper hypodermic doses correct all the metabolic disturbances of diabetes mellitus.

Banting's first papers were published (with Best) in the *Canadian Medical Association Journal* for March, 1922, and in the *Journal of Laboratory and Clinical Medicine* for February, 1922. The chemical process has been withheld as the property of the University of Toronto. This institution licenses dealers to manufacture the new preparation, which is called *insulin.* The Nobel Prize in medicine for 1923 was awarded to Dr. Banting and Professor MacLeod for this splendid achievement.

It remains still to identify insulin chemically, and to manufacture it synthetically. In view of the completeness with which insulin corrects the metabolic faults of diabetes, the question of additional internal secretions by the pancreas has not so far been raised.

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[1] Jour. Biol. Chem., 1916, **27**, 528; 1916, **28**, 286.

The most complete short account of the studies of the Toronto workers is given in the *Proceedings and Transactions of the Royal Society of Canada* (1922, 16, 27, 3d ser., Sec. 5).

The *process of preparing the extract,* free of proteins, lipoids and salts, without destroying the active principle is in part as follows (condensed quotation):

"Equal amounts of 95 per cent alcohol and minced pancreas are mixed and shaken, then allowed to stand. The mixture is strained through cheesecloth and filtered. Two volumes of 95 per cent alcohol are added, causing further precipitation of proteids, while the active principle remains in solution. The proteid is filtered out again, and the filtrate concentrated by distillation at 18° to 30° C."

This filtrate is treated with sulphuric ether. Further processes finally separate a substance which contains a minimum of proteid; is free of salts, and can be made isotonic. "It is free of lipoids. It is free of all alcohol-soluble constituents. On injection it causes no local reaction."

To work out a *method of standardization* the effect of insulin on the blood sugar of normal rabbits was studied. Insulin injected into normal rabbits lowers the blood sugar from the ordinary figure, 0.133 per cent, to figures far below this. A "rabbit dose" (subcutaneous) lowers blood sugar 50 per cent in one to three hours. "Sometimes after injection of insulin rabbits show symptoms of excitement followed by coma, rapid breathing, dilated pupils and interrupted by violent clonic convulsions. These frequently end in death from respiratory failure." This train of symptoms is due to hypoglycemia, as was presently found. The maximum per cent of blood sugar at which convulsions appeared was 0.047; the minimum at which they failed to appear was 0.037. Glucose injections immediately restored the animal to normal.

Studies of the respiratory quotient in diabetic dogs and men showed that insulin restores the altered quotient to normal. Insulin increases the deposit of glycogen in the liver and heart muscle of diabetic dogs, reduces the quantity of fat emulsion in the blood and diminishes or arrests the formation of ketone bodies.

Another observation noted early in these studies, and frequently confirmed by others, is that the hypoglycemia following insulin injections can be converted into a hyperglycemia by subsequent injection of epinephrine. This point will be alluded to again in the chapter on Gland Relationships.

DISEASES OF THE PANCREAS.

INFLAMMATIONS AND NEW GROWTHS.

Inflammations of the pancreas are a large subject. As they bear only secondarily on the problem of the internal secretion of the gland, a brief sketch must suffice here. For full details the recent text-books of medicine may be referred to.

ACUTE PANCREATITIS.

A rapidly fatal pancreatic hemorrhage may be the first sign of trouble. The patient, who has been apparently perfectly well, is suddenly seized with pain in the upper abdomen. The pain is colicky, sharp and severe. Nausea and vomiting accompany it. The bowels are constipated. The patient is cold, anxious, restless, and can only with difficulty be kept in bed. The belly becomes tender and tympanitic. Death is not long delayed. Autopsies have shown the pancreas acutely infiltrated with blood. Sometimes the hemorrhage is associated with cancer, and a large hematoma is found.

Acute pancreatitis *without hemorrhage* is a dangerous and not very uncommon condition. The symptoms resemble those of the hemorrhagic form, being only less severe and less rapidly fatal. The etiology is obscure. Bacterial infections are sometimes evident, secondary to blocking of the pancreatic secretion by a stone (gall stone or pancreatic calculus) lodged in the ampulla of Vater. The diagnosis of acute peritonitis, or gall stones, or intestinal obstruction, or perforation of a gastric or duodenal ulcer, is usually made. Treatment is expectant. Exploratory laparotomy has been done, without apparently much increasing the risk to the patient's life. Osler has reported the complete recovery of one such patient.

Suppurative and gangrenous pancreatitis are later complications.

Chronic pancreatic cirrhosis is often observed in elderly patients dying of other diseases. The pancreas is hard, small and nodular. Glycosuria may or may not be noted.

Syphilis of the pancreas has the pathological marks of organ syphilis in general. It also may or may not be accompanied by diabetes.

Pancreatic cysts and calculi occur.

Malignant disease of the pancreas is also to be met with. The common form is cancer of the head, blocking the common duct and producing severe jaundice, with voluminous, gassy, whitish stools containing undigested fat. Diabetes is a rare complication.

DISEASES OF THE INTERNAL SECRETION OF THE PANCREAS.

HYPERSECRETION. (HYPERINSULISM.)

There is some discussion in recent years of this possibility. Hypersecretion might readily occur temporarily in patients who are fasting and hungry, and are excited by the sight or smell of food. Seale Harris[1] has seriously suggested that the condition may not be entirely theoretical. A more permanent condition might be induced by hyperplasia or adenoma of the pancreas or the islet tissue, if one may reason from the analogy other glands offer. The symptoms in theory would be a mild chronic reproduction of the symptoms induced in rabbits and men by excessive doses of insulin—weakness, "nervousness," sweating, and in extreme cases unconsciousness, or faintness, with convulsive attacks. Much more work, however, must be done on blood-sugar figures during fasting before this suggestion can be more than a rational speculation. Further study may show that when time is sufficient the animal organism can always start up the automatic corrective mechanism, just as increased sweating lowers the rising temperature of violent exercise.

Diagnosis.—The diagnosis might be based upon the suggestive symptoms and upon the blood-sugar figures; these would run from 0.04 per cent down.

Treatment.—Treatment would be simple enough—administration of carbohydrate.

HYPOSECRETION (CHRONIC HYPOINSULISM). PANCREATIC DIABETES. DIABETES MELLITUS.

This subject is one of such extent and importance that the discussion of it has long ago grown beyond the limits of a single volume, much more of a single chapter. The following sketch is a brief outline only—to preserve the perspective and complete the scope of the present volume.

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[1] Jour. Am. Med. Assn., 1924, **83**, 729.

Definition.—Diabetes mellitus is a disease of metabolism, beginning with a failure to oxidize carbohydrate and presently also involving the metabolism of protein and fat. Its first signs are persistent hyperglycemia and glycosuria due to a failing supply of pancreatic insulin.

Etiology.—All ages, all races and both sexes are affected. The disease is commoner in men than in women, and is more often seen after the thirtieth year than before that time. It is not, however, very uncommon in children, and may even be congenital. Cases in early life are apt to be severe and more rapidly fatal.

As noted all races are affected. The disease is well known among the Chinese. It is especially common among Hebrews. Whether the Hebrew predisposition is hereditary, or is merely due to racial dietetic habits, is unknown. The appearance of diabetes in husband and wife *(conjugal diabetes)* is not very unusual, and among blood relations in the same family it is rather frequent.

Clinically it has been long known that stout people are more prone to diabetes than thin ones. This possibly is only because both conditions are generally the effects of a common cause, overeating. Overeating, especially overeating of starches and sweets, is a common antecedent, and when long continued seems to overstrain the glucose-converting power of the pancreas, leaving that organ in a state of relatively permanent fatigue, and the unconverted excess of sugar in the blood, when it has risen above a certain height, passes through the kidneys into the urine.

Organic changes in the pancreas are often noted at autopsy; sclerosis, in the general and inclusive sense of the term, is the commonest finding. But there are many sclerotic conditions and many tumors of the pancreas in which diabetes is absent. An attempt has been made to discriminate between ordinary pancreatic sclerosis and a form especially confined to and destructive of the islands, the latter form being supposed always present when diabetes occurs. But this is speculative. When the islets, as often happens, look normal under the microscope, it has been even proposed to *count them*, and attribute the incidence of diabetes to a deficiency in number rather than quality. A more satisfactory view is that, as with other ductless glands, there are sometimes circulatory and chemical changes at work—changes inaccessible to microscopical diagnosis. One should, however, note the claim of F. M. Allen,[1] that hydropic degeneration of the islets is a specific diabetic phenomenon, enabling the microscopical diagnosis to be made, and establishing them as the seat of the trouble.

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[1] Jour. Metab. Res., 1922, 1, 5.

Among the acute inflammations of the pancreas only syphilis requires special mention as a cause of hyposecretion.

Symptoms.—The patient is thirsty. He drinks more water than formerly, and notices that his urine is increased in quantity and that he has to rise frequently at night to empty his bladder. He is hungry; but in spite of the fact that he eats eagerly, he grows thinner, feels weaker and notices that his daily tasks are performed with increasing effort.

The urine on examination is found to contain sugar. This sugar is *dextro-rotatory glucose,* commonly written d-glucose, $C_6H_{12}O_6$, and is present in quantities varying from traces to 5 and 6 per cent or more in the twenty-four hours' collected specimen. The quantity of urine is usually increased, running from 4 pints to 8 and 10 quarts (2000 to 10,000 cc.) per day. The specific gravity is high (1.025 to 1.040), color pale and reaction acid. There is no albumin early in the disease, and the microscopical findings are normal. In later stages in older people albumin and casts appear, indicating the onset of Bright's disease, while the urinary sugar diminishes in quantity. Ketone bodies, indicating an acidosis, may or may not be present. When the patient fasts for one or two or more days the urinary sugar disappears and ketone bodies increase, or if previously absent now make their appearance. Acidosis, however, in the absence of glucose in the urine and of excess of glucose in the blood, is not a symptom of very great gravity; it may be only a starvation acidosis.

The blood sugar in diabetes is increased in amount. A summary of the important facts is given in a more convenient place under Treatment.

Metabolism.—In earlier stages and milder forms of the disease sugar will disappear from the urine if carbohydrates only are omitted from the diet. In severer cases the organism makes sugar from the proteins of the food as well. Fatty foods of ordinary molecular constitution (the details of *intarvin* may be found in the specialists' works) also are incompletely broken down, causing the appearance in the blood of a pathological fat emulsion, in the blood and urine of various ketone bodies (diacetic acid, β-oxybutyric acid and others), and imparting to the breath a sweetish fruity smell, which, in spite of the remonstrances of Professor Folin, physicians still persist in calling the smell of "acetone."

This condition of faulty fat metabolism is called *acidosis.* Acidosis is not confined to diabetes. It follows normally upon starvation; it is common in the gastro-enteritis of children; it is sometimes observed after the giving of a general anesthetic. In later stages of diabetes it appears paroxysmally, and the patient becomes cold, unconscious and finally profoundly comatose—diabetic coma. This state is usually followed by speedy death, unless insulin in proper doses is injected.

Complications.—The important complications of diabetes are cataract, diabetic retinitis, impotence and sterility, tuberculosis of various organs, a predisposition to various suppurative infections of the skin, such as boils and carbuncles, and a tendency to localized gangrene. Acidosis and coma may also be called complications, though they are rather symptoms of a severe type of the disease.

Carbohydrate Tolerance.—In diabetes as a clinical problem it is desirable to find out for each patient at the time of beginning treatment his *tolerance for carbohydrate.* This phrase means merely the largest daily amount of carbohydrate food he can take without causing hyperglycemia. It is a beneficent fact (discussed further under Treatment) that fasting increases the carbohydrate tolerance, and that anxiety, acute febrile disease and overeating reduce it.

Diagnosis.—The diagnosis of diabetes mellitus should be made not upon the urinary findings alone, but also upon the quantity of blood sugar.

As regards urinary tests, only two need be mentioned—Fehling's and S. R. Benedict's—as usually necessary in a busy clinical laboratory. Benedict has devised two tests, a qualitative and a quantitative. It is of the qualitative only that I shall speak here. It is simple, satisfactory and often has to be taught to patients. The physician should be perfectly familiar with the details. The formula for the qualitative test solution may be found in all the text-books, and it may be made up in one's own laboratory, or at a little greater expense may be bought from some reputable wholesaler of chemicals. Eight drops of the suspected urine should be added to 5 cc. of Benedict's solution in a test-tube of ordinary size. The mixture should be shaken and then set in boiling water for five minutes. An opaque greenish, yellowish or reddish cloud indicates glucose. In the laboratory a glass beaker may be used for the boiling water; the patient will find it easier to use a tall, enamelled saucepan, and employ the kitchen range or a gas heater in the bathroom. Milk sugar, an excess of creatinine, pentose and some drugs will give the same reaction. In cases of doubt the fermentation test with brewers' yeast should be used. A diagnosis should never be made on a doubtful reaction.

Personally, I must confess to some partiality still for Fehling's test. Taking 2 cc. each of Fehling's copper, Fehling's alkali and urine, and giving the test a "square deal," that is, placing the tube in boiling water for five minutes along with the Benedict tube, I have never seen it negative when Benedict's was positive. It also gives valuable quantitative information. If the above proportion of urine gives complete decolorization of the mixture, 1 per cent or more than 1 per cent of glucose is present. As pseudo-reactions rarely or never make so much impression as this on the blue color, one may conclude in such a case at once that sugar is present.

In trying out one's solution with measured amounts of glucose one should remember that many samples of "C. P. glucose" from the chemists contain water, the formula being $C_6H_{12}O_6+H_2O$.[1] Consequently, noting the molecular weights, 198 to 18, such glucose is one-eleventh short weight.

Some common sense must be exercised in the collection of urinary samples. For example, many chronic diabetics do not pass sugar in the morning urine. This sugar-free morning evacuation may be large in amount, and in a twenty-four-hour sample may excessively dilute the sugar passed at other times, making it harder to test for. Moreover, few patients know how to keep a twenty-four-hour sample from growing foul, and some putrefactive organisms break down glucose very fast, so that the test may be further obscured. It is, therefore, usually better to have the patient empty his bladder just before a test-meal, and bring a sample passed two hours after. Even within one hour after the ingestion by a diabetic of 75 or 100 gm. of starch or sugar, when no preceding fast has been instituted, the urine is apt to show glucose in considerable amount.

As regards a test-meal, authority and prejudice have dictated this and that kind of food, but the only essential is that the food should be assimilable carbohydrate. Wheat bread, potato, cane sugar, rice or glucose may be given, or a mixture of these—the total quantity in doubtful cases not to be less than 75 gm. Often no test-meal is necessary, the patient running an abundance of sugar on his ordinary diet.

With ignorant patients frequenting free clinics it is common to encounter urinary samples in cough-syrup bottles which have not been washed free of their former contents. Many foolish mistakes are made in this way, as glucose syrup is a frequent base for cough mixtures.

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[1] Remson, Ira: Organic Chemistry, 5th revision, New York, D. C. Heath & Co.

Nursing mothers and those whose breasts are distended with milk for a week or more after weaning the baby frequently have in the urine well-marked traces of milk sugar, and the copper reduction test will be prompt and confusing. When this possibility is present the urine may be fermented with brewers' yeast, or the test-meal may be given, or the blood sugar may be determined.

Taking up now the matter of blood sugar, I must first express a regret that the matter is not more popular with general practitioners than it is. A well-known and successful laboratory man in New York told me recently that he did not get a call for a blood sugar once in three months. Perhaps the question has been made needlessly difficult. Personally, I feel that every physician treating diabetes should have his own laboratory and do his own blood sugars. When many tests are to be done the patients should come in a group on a special day; the work is easier thus, and the time consumed is reduced to a minimum.

Perhaps the commonest method in use today is the Benedict method simplified from the Lewis-Benedict method of ten years ago. This test is only a clinical approximation, but is to that extent reliable and satisfactory. I have worked out some simplifications of the test which reduce the time it takes to about fifteen minutes and detract virtually nothing from the clinical accuracy of the result. The picric acid-picrate solution should be titrated before using, and if not accurately $\frac{1}{20}$ normal acid it should be made so with acetic acid or NaOH, using a phenolphthalein indicator. The "anhydrous" Na_2CO_3 is troublesome to prepare, and one may use Squibb's so-called "anhydrous carbonate," which contains about 27 per cent of water, and then allow for the water by a proportion in arithmetic before weighing. One can also save bother in chilly laboratories in winter by using 2 cc. of a 10 per cent instead of 1 cc. of a 20 per cent solution of carbonate. The latter crystallizes out a little below 60° F. And in respect of colorimeters, the Dennison instrument, devised by Peebles and Lewis,[1] and costing $1.00, is quite a handy and satisfactory substitute for the Duboscq or other expensive apparatus sold by the dealers.

Many other reliable blood sugar methods are to be found in the text-books. S. R. Benedict[2] describes a new process indicating that all present methods give excessive figures.

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[1] Jour. Am. Med. Assn., 1918, **70**, 679.

[2] Jour. Biol. Chem., 1925, **64**, 207.

Passing on from this brief note on technique to the clinical side of the subject, we need remember only a very few facts, namely, that "normal" blood-sugar percentages range around 0.1 per cent and that the "threshold" value in diabetes, *i. e.*, the level of blood sugar that causes glycosuria, ranges all the way from 0.155 per cent in early cases to 0.35 per cent or more in cases of longer duration. H. O. Mosenthal[1] has suggested that this later rise in the threshold of renal permeability is possibly an automatic effort on the part of the organism to protect itself, giving the blood sugar more time to oxidize before excretion. The facts at all events are well known.

The diagnosis of diabetes mellitus is only to be made when under prescribed dietetic conditions the urine shows glucose, and the blood sugar is persistently higher than normal.

There are some perplexities, but not many, if we allow ourselves time for observation. As regards "renal diabetes" not much is known. The consensus of opinion in later time is that it is very rare but may exist. There is a true glycosuria, moderate and fairly constant, but the blood sugar is normal, and the urinary sugar is little or not at all influenced by overfeeding of carbohydrate. Cammidge has reported 2 cases, father and daughter; a half dozen cases are to be found in recent American literature (D. S. Lewis[2]).

Blows on the head sometimes cause glycosuria for a few days or weeks. A little girl, aged five years, in my care, once had over 1 per cent of sugar in her urine after a fall from a fire escape. The condition continued for three weeks and then disappeared. The patient is still in perfect health, fifteen years after. Other causes of glycosuria not primarily associated with the pancreas are mentioned on page 264.

Prognosis.—Recovery is not the common thing in diabetes. In patients who have "recovered" a more careful analysis of the case indicates that the diagnosis was in error. In older patients, however, the prognosis is not as a rule very grave. In young adults and in children diabetes tends to be more rapidly progressive, and the outlook for long life is bad. When the treatment is rational, and the patient's good-will sincere, the prognosis is proportionally improved. Surgical operations (even the extraction of teeth) should be performed with conservatism, and only after careful dietetic preparation. A long etherization may precipitate a fatal attack of coma.

The discovery of insulin has greatly added to the hopefulness of the prognosis. The skilful use of this remedy insures indefinitely against the more serious accidents and complications of the disease. By the prompt use of insulin even coma may be recovered from, and in young persons and small children with little or no tolerance for carbohydrates insulin works miracles.

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[1] Tice's Practice of Medicine, 1920, vol. **9**.

[2] Arch. Int. Med., 1922, **29**, 418.

Treatment.—Coming finally to the question of treatment, I do not propose to go into the multitude of text-book details, but only to emphasize some special matters which have interested me most. I shall begin with a few comments on certain wrong ways of treating the disease.

Going back over the notes of the last half dozen years I find nothing more discouraging than the persistent impression of the laity, and of far too many physicians, too, that gluten bread is a safe food for the diabetic. As far back as 1906 the U. S. Government *Bulletin* (No. 28) of Professors Atwater and Bryant published analyses of gluten bread, showing that it contains on an average 49.8 per cent of carbohydrate. Yet, through the selfish efforts of the manufacturers, quantities of it are still sold on the East Side of New York to ignorant patients—often at the instance of misinformed practitioners.

Another real misfortune is that rolled oats, once long ago so loudly extolled by von Noorden, is still believed by some doctors to make a safe diabetic diet. Where this is true once, it is entirely untrue at least twenty times; every patient should be carefully tested on small amounts of it before it is written into his regular diet.

Another unfortunate fact is that many doctors who treat or attempt to treat diabetes refuse to learn and do in their own laboratories the necessary chemical work. There are, of course, numerous chemical matters in diabetes which must be reserved for a chemical specialist in a well-equipped professional laboratory, but the clinical management rarely requires more than blood sugars, urinary sugars and acidosis tests. When a competent assistant is not available, the physician will find excitement and satisfaction in doing these tests himself, and of course he should charge a fair price for the work, just as he does for his office work. Joslin[1] has very justly noted that surgeons spend thousands on good operative apparatus, while physicians are reluctant to spend $25.00 for the "layout" necessary to take proper care of their diabetic patients.

Then there are the doctors who tell me they have "no time to bother with calories," and the doctors who think once in three months is often enough to see their diabetic patients, and the doctors—but perhaps I have said enough of the failings of a too much abused profession; I will pass on.

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[1] Treatment of Diabetes, 3d ed., Philadelphia, Lea & Febiger, 1923.

The aim of treatment in diabetes is to keep the urine free from sugar, and the blood sugar within normal limits. That treatment is possible at all is due to the fortunate and beneficent fact that abstinence from food increases the carbohydrate tolerance. Sometimes it is enough to let the organism rest from starch and sugar only; sometimes it is needful to cut down the proteins and fat as well; generally one must not merely cut down but *withhold* all food until the urine is sugar-free and the blood sugar has made a material drop. This basic fact in the management of diabetes has been popularized and developed very largely in recent years by Frederick M. Allen,[1] and while fads and fancies may modify it, I imagine that in essentials it will always be a monument to Dr. Allen's great services to diabetic sufferers.

The details of fasting may be found in all the recent text-books. I can only make a few comments by the way. One is that the patient often tires very soon of broth. A reasonable appeal should be made to his palate by seasoning the soup with a minute amount of various green vegetables, and often changing the meat base. Also, the patient should be taught good habits at the start by provision of a scale, upon which he should weigh everything he eats. A gravity scale is the proper thing to use, a driking glass being put on one pan with water enough in it to balance the dinner plate on the other. The department stores sell a small spring scale for $2.88. This is marked in ½ ounces (about 15 gm.) and is just as serviceable as the popular $10.00 gram spring scale; indeed, as far as I have observed, it lasts longer without getting out of order. An inaccurate scale is a source of grave danger in difficult cases.

Not only the patient should know his calorie values, but the physician as well. I have know of some well-taught patients who derived much quiet amusement from the dreadful mistakes their doctors made every day in calorie values.

As a source of information in calorie values I find the revised *Bulletin* (No. 28) of the U. S. Department of Agriculture the most reliable document. I do not encourage patients and nurses to carry about and copy from hand to hand illegible and complicated details of calorie values. Serious mistakes are often made, which react directly on the physician's success and reputation.

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[1] Glycosuria and Diabetes, Boston, W. M. Leonard, 1913, and *passim* in more recent medical literature.

After a few days of green vegetables, 1, then 2, then 3 eggs may be allowed, then a little lean and fat meat and butter, and finally a few grams of carbohydrate.

In respect of carbohydrate, nothing is so dangerous as "skating on thin ice." One's object is, of course, to push along the carbohydrate tolerance as fast as possible; but tolerance increases very slowly—not by days but by weeks and months—and one should prescribe only about one-half as much as one thinks the patient will carry, and increase this amount only about one-half as fast as one would like to.

I have already mentioned that the Benedict test for glucose in urine may be often usefully taught to patients. Sometimes they cannot do it, sometimes they will not; but when they can and will, they should make a daily test at home of urine passed two hours after the heartiest carbohydrate meal. Whenever sugar is found the patient must starve again for three meals.

The *crux* of the problem in diabetes is to secure the patient's coöperation until such time as he has acquired *fixed habits of abstinence.* When one recalls that the cry for food is the basic motive throughout the whole animal creation, and that through countless ages *hunger* has antedated every other fact of consciousness in the slowly evolving mentality of man, one should not be too cross when the sufferer breaks diet, as he very generally does. Self-control is a rare virtue even among the educated, and among the working people a treatment that first of all forbids the lunch of bread and glass of sweet coffee for breakfast seems simply impossible. They tell you so not exactly in the words of the poet, "Better fifty years of Europe than a cycle of Cathay," but in language far more unmistakable! Yet, for these patients, even after months of discouraging failure, there is still sometimes hope. The specialists try to get the patient started in the straight and narrow way by housing him for three months in an expensive hospital where he has companions in distress. But even with those whose means admit of this, a return to the ordinary affairs and conditions of life often brings temptations which are irresistible. The patient's family are often his worst enemies. And if he is an unmarried working man, and must live in restaurants and cheap boarding houses, he cannot command his prescribed diet for any sum he can afford to pay, and he soon gives up trying.

Even upon the obedient patient there are many accidents of daily life which bear hard. An attack of tonsillitis, of influenza—any intercurrent febrile affection -starts up glycosuria, and a ten-day attack of measles in a diabetic child sometimes completely destroys his carbohydrate tolerance for a long time. Business anxieties are also an enemy to carbohydrate tolerance, and even such a trivial matter as the severity of the winter temperature makes a marked difference in the welfare of some patients, warm weather making a smaller demand for calories.

There are also many obedient patients of advancing years who in the lapse of time do badly for the very reason that they are obedient. It is easy enough to work out a pleasing scheme in grams of proteid and of fat which will provide the desired number of calories per day; but the unfortunate fact remains that man in the temperate zones requires normally just twice as much carbohydrate as he does proteid and fat combined, the proportion being, roughly: Fat, 1; proteid, 1; carbohydrate, 4. In consequence, while younger patients sometimes successfully readjust their metabolism to the new ratios, the extra proteid burden in older patients very soon overworks the kidneys, and though sugar disappears from the urine, albuminuria starts up, the blood-pressure rises, albuminuric retinitis presently obscures the patient's vision, and the last state of that man is worse than the first—Bright's disease has set in.

To prevent or retard this unfortunate occurrence one should be always on his guard. Every such patient should be carefully re-studied from time to time. All bacterial foci—old spongy tonsils, bad teeth, chronic cystitis, intestinal stasis, infections of the bile tract—should be attacked. The question of syphilis should be carefully considered in every case. A full allowance of carbohydrate should be carefully assured (watching the blood sugar rather than the urine), and the total proteid and fat supply cut down until the patient's weight has been materially reduced. Many fat diabetics of advanced age can easily fast two days in the week with advantage. It is apparent to any careful observer that fasting benefits many cases of Bright's disease who never had diabetes, so that such a therapeutic procedure helps in both directions. A salt-free diet is also to be strongly advised when the systolic blood-pressure stays over 190.

Every new patient with sugar in his urine *presents a new problem.* The patient and not the disease must be the first thought. The confidence of the patient must be gained as soon as may be, and diabetic restrictions must be tactfully and sympathetically imposed. No case is absolutely hopeless until the patient goes into coma. The worse diabetics sometimes do wonderfully well. One should not, therefore, begin by assuring the patient that his case is of great gravity, and that there are no prospects of cure. A witty youth, later in my care, wrote to his former physician, who had probably talked rather pessimistically about his condition: "Dear Dr. P.:—After you told me the other day that I was in a bad way, and that you could not promise anything in the way of improvement, I went to a restaurant and by way of *reprisal* I ate four slices of pound cake and a peach 'Melba.'"

If you can once gain your patient's confidence, and convince him of your personal interest in his welfare, the therapeutic problem is more than half solved.

Medicinal Treatment.—Leaving to the specialists the enumeration of drugs and surgical procedures occasionally contributing to the cure of diabetic complications, I shall mention only the endocrine treatment.

Fresh pancreas by the mouth was tried many times. Many commercial extracts were advertised in former years. None ever stood satisfactory scientific and clinical tests.

In a paper[1] read before the Medical Section of the New York Academy of Medicine some years ago I described fully the chemical process, and reported some clinical experiences in the use of a new pancreas extract which I still employ with satisfaction. I believe it to be of value in diabetes. It appears without question to increase the carbohydrate tolerance in those early cases of diabetes in which nothing but the carbohydrate mechanism has gone wrong.

In carefully controlled laboratory tests the extract that I speak of will cause, in two hours in the incubator, the disappearance of a considerable part of a measured amount of glucose added experimentally to defibrinated fresh blood. No other visceral extract behaves in this way. In a long series of blood-sugar tests on patients the extract was found to cause a pronounced blood sugar fall in 82 per cent of the cases observed within two hours after administration by mouth. Controls of about an equal number of patients under the same clinical conditions, as far as this was possible, showed a fall in less than 40 per cent. I therefore think my formula of proved benefit, apt to be useful in all cases, and especially so in the earlier cases. The standard tablet is $\frac{1}{3}$ gr. of extract in 4 gr. of bicarbonate of soda. The dose is usually three tablets after each meal—nine a day—but much more may be given. The bottle should be dated, and the contents not used after six weeks, deterioration being probable after that time. It is for sale by several New York wholesalers.

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[1] Med. Record, March 3, 1917.

While I think this remedy of value in chronic cases by reason of its cheapness and easy oral administration, no one is more ready to acknowledge fully the perfect clinical success and universal applicability of Dr. Banting's discovery, insulin.

Insulin.—The history and some of the properties of this preparation have been mentioned on another page. Now that sufficient experience has confirmed its genuineness and its wonderful efficiency in diabetes, there is time to realize its limitations. The necessity of giving it by hypodermic injection, and the danger of too large a dose, have made the profession rather advise its use only in the severer cases, or in cases complicated by gangrene, tuberculosis, other febrile diseases, carbuncle, or threatening acidosis.

Insulin, as already noted, it is now made by various dealers under license of the University of Toronto. The Toronto Committee expect the manufacturer to furnish, along with the remedy, a circular[1] containing the following information or its equivalent:

"Insulin, as at present supplied, is an aqueous solution of the active principle obtained from the islands of Langerhans in the pancreas. It is made under license from the University of Toronto which controls the product. This extract when injected subcutaneously enables the diabetic patient to utilize carbohydrates in a normal manner. Insulin is quite stable and will keep at room temperature.

"The strength of insulin is measured in units. The amount of glucose which 1 unit of insulin will enable the body to utilize varies in different patients and under different circumstances, but the amount is usually 1 to 2 gm. per unit. The number of units contained in each cubic centimeter is clearly stated on the label of each package. The method of standardization now used is quite reliable, but does not prevent a variation of 5 to 10 per cent in the finished product. The patients should be kept under competent observation, and their diet, insulin dosage and sugar excretion checked frequently by the physician.

"Insulin, when given too long before a meal, or when given in too large a dose, will cause a lowering of blood sugar below the normal level—a hypoglycemia. This is to be avoided, as too great a lowering will cause acute symptoms, such as weakness, nervousness and sweating. These early manifestations if not promptly treated may be followed by drowsiness, stupor and, possibly, serious results. The early symptoms must be promptly overcome by feeding the patient some form of available carbohydrate, preferably orange juice, glucose or cane sugar. Even when the patient is stuporous, if glucose or sugar can be administered by mouth or by stomach tube, recovery is remarkably rapid. If it is impossible to give carbohydrate in this manner or if the patient is in a critical condition, from 5 to 20 gm. of glucose should be injected intravenously using a 5 to 50 per cent sterile solution. This restores the blood sugar and the patient recovers and returns to normal usually within ten to thirty minutes.

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[1] By courtesy of Messrs. Eli Lilly and Co., I quote the following paragraphs.

"This remarkable lowering of blood sugar by insulin makes necessary extreme caution in its administration. Generally speaking, it is best given twenty to thirty minutes before a meal, either once, twice or three times daily, according to the severity of the diabetes. The blood sugar removed from the blood stream and stored or utilized through the influence of the insulin is thus in part replaced by the carbohydrate absorbed following the meal, or to state it in another way, the high blood sugar which usually follows the ingestion of food is prevented and in the diabetic the usual excretion of excess sugar in the urine does not occur because the carbohydrate is being rapidly stored or utilized by the body.

"In those cases receiving insulin without adequate laboratory control of blood sugar it may be safer to have a blood sugar somewhat above the normal at some period of the day with a transient glycosuria than to have the urine continuously sugar-free with a blood sugar below normal. However, in these cases, if the patient be properly informed of the early symptoms of low blood sugar (weakness, nervousness and sweating), and is instructed to have always in his possession some form of sugar for immediate consumption, the danger from insulin will be minimized. Orange or other fruit juice, corn or glucose syrup, sugar or candy afford readily available forms of sugar capable of acting rapidly as an antidote for an overdose of insulin.

"Insulin is only an adjunct to the dietary treatment of diabetes and as with diet so with insulin, the success attained will depend largely on the intelligence and coöperation of the patient.

"The dose should be stated in units, and the number of units in each cubic centimeter should be carefully noted on the label of each vial before the solution is withdrawn.

"Do not remove the stopper. Cleanse top of rubber stopper with alcohol; have needle and syringe sterile; draw air into syringe equal to dose to be given; insert needle through stopper, invert ampoule and force air into ampoule and then withdraw required dose. Rub skin at site of injection with alcohol and inject deeply into the subcutaneous tissues but not intramuscularly."

After carefully noting this information, it will be seen that the administration of insulin is a matter of ordinary clinical intelligence applied individually to each successive patient. No larger equipment is exacted from the practitioner than formerly, except that he shall provide for the more frequent estimate of blood sugars.

It has been noted on page 248 that proper doses of epinephrine by hypodermic will raise the percentage of blood sugar in the hypoglycemia from an overdose of insulin. This may be at times a practical clinical resource. J. H. Burn[1] has reported that in rabbits the hypoglycemia of insulin may also be raised by injections of posterior pituitary extract.

Various specialists have worked our elaborate printed schemes of foods, calories and number of injections of insulin. All these require modification for each patient to such an extent as to make them of only relative value. Any physician, I repeat, can give the insulin treatment to his diabetic patients with safety and satisfaction if he has a convenient place at hand where he can do or have done a sufficient number of blood-sugar tests.

In emergencies when blood-sugar testing apparatus is far away, E. P. Joslin has made the useful suggestion that the medical attendant may continue to give small doses of insulin as long as the patient is passing sugar in the urine. When the patient is delirious or unconscious a catheter may be used every little while.

The caution of the Toronto Committee in the matter of overdosage is of course commendable, but in actual practice death from insulin hypoglycemia has been a very rare accident. Personally I have heard of but one.

In respect of insulin, many chemical researches are now going forward. It is quite possible that its precise formula will be presently announced, and that a synthetic process for its preparation can be devised. A form of it administrable by the mouth is a *pium desideratum* that seems further off.

Note on Glycosuria.—This seems a convenient place to add that there are numerous additional causes of glycosuria which have nothing primarily to do with the pancreas. Pollak[2] has summarized them as follows:

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[1] Jour. Physiol., 1922–1923, **57**, 329.

[2] Arch. f. exp. Path. u. Pharmakol., 1909, **61**, 376.

The drug phlorhizin, derived from the bark and root of apple and cherry trees, when subcutaneously injected causes a glycosuria which seems to be due to an alteration of the permeability of the cells of the kidney. The blood sugar is not raised. "Glycosuria continues after all the stores of glycogen are exhausted, and the blood sugar stands if anything below normal" (Macleod[1]).

Renal poisons like uranium salts also cause glycosuria without raising the blood sugar.

Certain laboratory experiments upon animals first raise the blood sugar, and then cause glycosuria. Among these are puncture of floor of the fourth ventricle ("piqûre"), afferent nerve stimulation, asphyxia.

Injections of strychnine and caffeine act centrally, and adrenalin acts both centrally and peripherally to produce glycosuria.

To Pollak's list should be added the glycosuria arising from large injections of liquor pituitarii (p. 169).

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[1] Loc. cit.

CHAPTER IX.

THE INTERNAL SECRETIONS OF THE SEX GLANDS.

Introductory.—The scientific literature of the *sex glands*, or as they have been latterly called, the *gonads*, has grown to such size in recent years that a volume as big as a dictionary could not hold a list of even the more important references. To preserve the perspective of the present book only a short review of the more significant facts is possible, and of these only as they concern the sexual hormones.

By reason of the remarkable researches of recent times,[1] it has been possible in the fruit fly (Drosophila melanogaster) to trace back the origin of sex with considerable probability to differences in the chromosomes of the germ cells prior to conjugation, so that in the fertilized ovum the Mendelian factor for sex is already present. The conditions in vertebrates in general, and in mammals, are still in the controversial stage. It seems, however, certain that sex differentiation in the mammalian embryo is a very early occurrence. At birth there is a general similarity of bodily shape, with the primary and secondary sex characters of every individual, male and female, already perfectly adjusted for further extra-uterine development.

Scientific students long ago called attention to the fact that in early childhood both sexes occupy a relatively neutral sexual position. The internal secretions of the testis and ovary begin only very slowly to react upon the genitalia, the secondary sex organs and the somatic tissues, and to interact with other ductless glands so as to produce the complete sexual differentiation of adult years. The question can only be touched on here.

No better account of this process can be found that that by Havelock Ellis.[2] Although this volume was published a good while since, it requires but few corrections.

In view of the rather loose way in which the terms primary and secondary have been applied to sex marks, it may be well to state at once that the distinction is not a vital matter. Some writers call the generative cells *primary* sex marks, the organs of generation *secondary* and the other sex characters, such as breasts and beard, *tertiary*. A Lipschütz[1] calls this "terminological polemics," and suggests that the term "sexual character" should be alone used. He defines this as any character, of structure, or function, of mind or body, by which individuals of one sex differ from individuals of the other sex in the same species. The sum of these differences constitutes *sexual dimorphism.*

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[1] Morgan, T. H., and co-workers: Mechanism of Mendelian Heredity, revised ed., New York, Holt, 1923.

[2] Man and Woman: A Study of Human Secondary Sexual Characters, 5th ed., London, W. Scott, 1914.

Puberty in girls coincides with a notable speeding up of growth, an increase in weight, a hypertrophy of the breasts, a growth of hair over the pubis and in the axillæ, a characteristic development of the pelvis and distribution of the bodily fat, and the appearance of menstruation. Along with these bodily changes comes a corresponding change in the psyche.

In boys the *crines pubis* is more extensively developed over the belly—even as high as the navel—than in girls; hairy growths over the limbs and trunk generally thicken, and face-hair begins to appear. The larynx enlarges, and the voice grows in volume and drops in pitch. The mental grasp increases, and the more serious problems of human existence begin to present themselves in consciousness. Finally, fully developed flagellated spermatozoa appear in the seminal vesicles, and erections and ejaculations are possible.

So marked and striking are these changes that in German scientific literature the sex glands are now often called *die Pubertätsdrüsen*, "puberty glands." However, the internal secretions of the sex glands continue profoundly to influence the human mind and body long after puberty. Though woman's climacteric at forty to fifty years is externally signalized only by cessation of the menses, it is probable that there is a gradual diminution in the internal secretion of the ovaries from that time. There is a loss of desire, a decline in mental activity, a diminished initiative, a slow lapse into habit-life, an increase in weight and a gradual approach of the physical signs of old age. Man also in many instances has a climacteric, and the decay of his bodily powers is quite scientifically set out by Shakespeare:

> "The sixth age shifts
> Into the lean and slippered pantaloon,
> With spectacles on nose, and pouch on side;
> His youthful hose, well saved, a world too wide
> For his shrunk shank; and his big manly voice,
> Turning again toward childish treble, pipes
> And whistles in his sound."

With this brief sketch of the general subject, we turn to the precise endocrine details.

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[1] Internal Secretions of Sex Glands, Cambridge, Heffer, 1924.

ANATOMY OF THE TESTES.

Elaborate and accurate descriptions are to be found in the standard texts. An excellent and recent short account is given by H. E. Jordan.[1]

The *testes* are two small glandular organs. They have both an external and internal secretion. They are suspended from the pubic bones and the spermatic cord in a sac covered with hairy pigmented skin called the *scrotum*. They are ovoid bodies, about 4 by 3 by 2 cm. in size, flattened from side to side, lying rather obliquely in the scrotum, and weighing from 20 to 35 gm. apiece. The left is heavier, and hangs lower. They have three coats—a *tunica vaginalis*, which is the peritoneal covering retained at the time of their descent from the belly, a *tunica albuginea*, and inside this a looser vascular layer of connective tissue.

They are abundantly supplied with vessels and lymphatics and have connections with the sympathetic and parasympathetic nervous systems.

Not True

The external secretion of the testis, *semen*, is carried by a long duct called the *vas*, or *ductus deferens*, to the *seminal vesicles* at the base of the bladder. The vas deferens is about 2 feet (66 cm.) long. It leaves the testis by way of the spermatic cord. The seminal vesicles are a convoluted mass of storage tubules. A common duct from vas and vesicles penetrates the prostate gland and opens on one side of the prostatic urethra close to the opening of its fellow on the other side.

Fine Structure.—The tunica albuginea (Fig. 46) is reflected at the rear edge of the testis into the interior of the organ, and makes a more or less complete partition in the gland called the *mediastinum testis*. Fibrous bands spread thence in various directions to the surface of the organ and divide it into many somewhat cone-shaped spaces. These are occupied each by two or three *tubuli seminiferi*. The tubuli seminiferi may be disentangled by carefully dissecting the tissues under water; when straightened out they may measure 1 or 2 feet (30 to 70 cm.) in length. As the older teaching was, they have a blind end and an open end, but their arrangement is possibly not always so simple as this. The open ends finally unite in the mediastinum testis to make twenty or thirty large straight ducts about $\frac{1}{2}$ mm. in diameter ($\frac{1}{50}$ inch), which ascend along the posterior border of the mediastinum, discharge into an adjacent retiform organ, the *rete testis*, and by conduction through an elaborately coiled system of tubules in an adjacent organ, called the *epididymis*, finally connect with the vas deferens.

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[1] Text-book of Histology, New York, Appleton, 1924.

The tubuli seminiferi are lined with several layers of cells. The deeper cells are *spermatogonia*. The nuclei of the spermatogonia are constantly undergoing cell division, and the superficial cells, the *spermatoblasts*, are presently detached, and carried off as *spermatozoa*, to be stored in the seminal vesicles. Finally it must be noted that the spermatoblasts are held in place by supporting or sustentacular cells called *cells of Sertoli*, or *trophoblasts*.

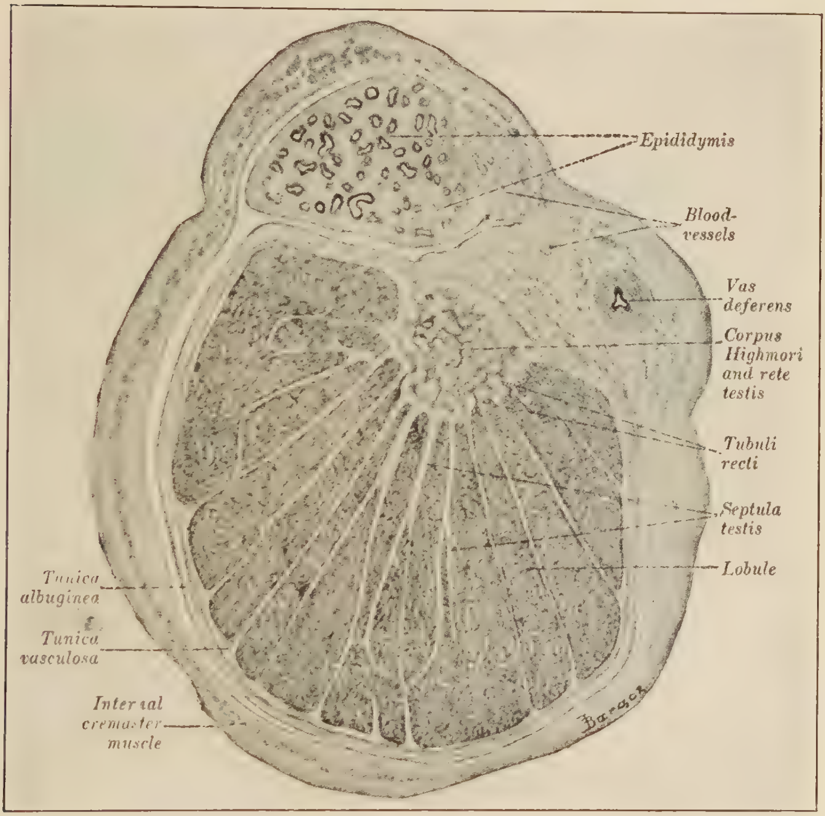

Fig. 46.—Transverse section of testis of boy, aged two and one-half years. × 7. (Szymonowicz.)

Supporting the tubuli seminiferi in the testis is found a peculiar type of connective tissue. This connective tissue contains cells to which for a variety of reasons the vital function of internal secretion has been assigned. Franz Leydig,[1] when privatdocent in Würzburg, described them first many years ago without attributing to them any definite function. He says only, "Der ganze Habitus ist so dass man von einer fertigen Zelle sprechen kann." In his *Text-book of Histology* (1857) he seems to have thought them merely connective-tissue cells, like those of fatty connective tissue. They have been since called "Leydig's cells," "interstitial cells," the "interstitial gland" (Bouin and Ancel), "die Pubertätsdrüse."[2]

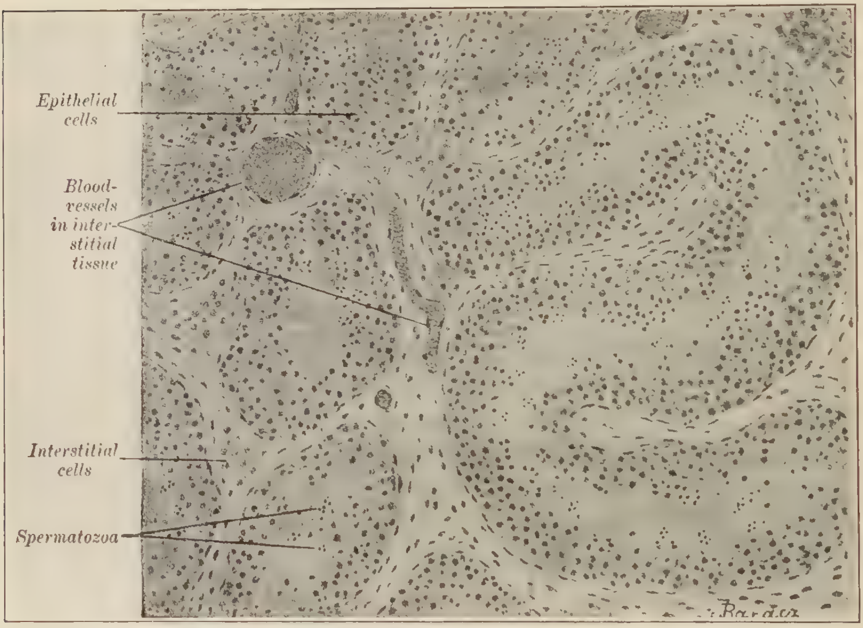

Fig. 47.—Transverse section of a human testis. × 125. (Szymonowicz.)

It may be stated at once that in mammals generally the identity of Leydig's cells as the source of the internal secretion of the testis is to this day not more than a probability. But for the time it seems to be the most convenient working hypothesis. The Nancy professors, P. Bouin and P. Ancel[3] are said to have first made the suggestion. They summarize the preceding literature, with references. A list of further and more recent references may be found in the admirable volume of A. Lipschütz,[1] who critically collates the arguments. (See also p. 272.)

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[1] Ztschr. f. wissensch. Zoöl., 1850, **2**, 47.
[2] Steinach: Pflüger's Arch., 1912, **144**, 71.
[3] Arch. d. zoöl. exp., 4. ser., 1903, **1**, 437.

Interstitial Cells.—The interstitial cells differ in size and shape from the common connective tissue cells of the testis. The interstitial cells stain well with ordinary laboratory dyes. The cellular protoplasm is abundant and the nuclei rounded and pale, with several nucleoli. In adult rabbits' and guinea-pigs' testes the cells occur in masses and cords. Their number varies with the species, *e. g.*, they are said to be relatively few in mice, very abundant in cats and wild boars. In man the interstitial cells lie in a connective tissue consisting only of fine filaments. Various inclusions have been described. Wagner[2] found in them the granulations noted elsewhere in secreting cells (see p. 18), and claimed that transitional forms between ordinary connective cells and interstitial cells could be easily made out. Lipschütz notes:[3] "If it is permissible to draw conclusions from histological appearance, one must presume that the interstitial cells are glandular," and he adds that the possibility of their embryological origin from mesoblast instead of from entoblast cannot stand in the way of such a view.

In respect of age, the appearances of the interstitial cells vary notably. In young embryos they are easily noticeable. In older embryos they seem smaller and less active. After birth, as far as observed, they retain their infantile appearance for a time and develop more rapidly again as puberty approaches. In adult men with normal testes the interstitial cells are always present. T. R. Goddard[4] found them very abundant in the retained testes of five young men, though the seminiferous tubules were atrophied; and in a man, aged seventy-eight years, large areas between the tubules were tightly packed with interstitial cells.

Ligation or partial excision (vasectomy) of the vas deferens causes a slow atrophy of the seminiferous cells, but seems to cause an increase, or perhaps only a relative increase, of the interstitial cells, without damaging the sexual characters. The undescended testis, as just noted, often contains an abundant supply of interstitial cells, and even with double undescended testis puberty may appear at the usual time. Roentgen-ray exposures have been proved to cause damage to or even complete destruction of the spermatogonia, leaving only a few cells of Sertoli in the seminiferous tubes; but the interstitial cells are not affected, and the general sexual character of the exposed animal remains unchanged.

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[1] Loc. cit.

[2] Anat. Anz., 1922 1923, **56**, 559.

[3] Loc. cit., p. 116.

[4] Jour. Anat., 1919–1920, **54**, 173.

Whether excision of one testis causes hypertrophy of the other, or removal of one and incomplete excision of the other, causes hypertrophy of the remnant, is disputed. Lipschütz[1] thinks that the physiological "law of all or nothing" probably holds, *i. e.*, that more than a threshold amount of secretory stimulus will fail to produce more than a normal reaction.

The eunuchoid state is found only in animals with absent testes or undeveloped interstitial cells, and "sexual maturity is possible even when spermatozoa were never present in the testes" (Lipschütz).

This array of facts reasonably supports the conclusion that the interstitial cells produce the internal secretion. If they do not, then the sex hormone must arise from the walls of the tubules or from the cells of Sertoli, for which there is insufficient proof.

Arguments and facts still advanced against the interstitial hypothesis may be found in recent papers by Berblinger,[2] by C. Sternberg[3] and by B. F. Kingsbury.[4] For the immense literature covering allied studies in birds (especially domestic fowls), fishes, amphibians, crustacea and insects, the text-books and journals of zoölogy may be consulted.

Embryology.—Except for hypothetical differences in the chromosomes of the germ cells the reproductive organs of the two sexes in mammals are indistinguishable in the youngest embryos. The gonads first appear as a *genital ridge* on the mesial side of each Wolffian body. This ridge is made by a thickening of the cœlemic (mesoblastic) epithelium, as stated by older writers; later students claim that the germ plasm is entoblastic. This epithelium is supported by a small mass of connective tissue. A morphological distinction of sex can first be made out above the seventh week. The ridge becomes partly separated from the Wolffian body, but still continuous with it by a *mesorchium* or *mesovarium*. The epithelium is the *primitive germ epithelium*, which by a complicated series of changes finally constitutes in the male the lining cells of the tubuli seminiferi and in the female the primitive ova of the ovary.

The details of the developmental process have been amplified to an enormous degree. Here it need not specially concern us whether the internal secretions of the testis and ovary are, or are not, of mesoblastic origin. If current researches are correct, the cortex of the adrenal is of mesoblastic origin, and the kidneys are entirely of mesoblastic origin.

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[1] Loc. cit., p. 166.

[2] Verhandl. d. deutsch. path. Gesellsch., 1921, p. 186, with references.

[3] Ibid., p. 197.

[4] Am. Jour. Anat., 1914, **16**, 59.

Descent of the Testis.—In the fifth month the testis is still in the lumbar region. By the end of the eighth month it has descended into the scrotum. At birth the passage-way from the belly is already closed. Sometimes in men, and in some mammals, the testis on one or both sides fails to descend, and the condition is called retained or undescended testis, or *cryptorchidism.* In some mammals (elephant, whale) it remains in the belly; in some it descends only at rutting time.[1]

Accessory Testicles.—Accessory testicles are in theory fully as possible and probable as accessory and supernumerary glands of other kinds. It seems highly unlikely that they do not sometimes occur. I can, however, find in recent literature no reference to their appearance except in a quotation by Jordan,[2] source not stated. Le Dentu[3] refers to one assured and several doubtful cases.

PHYSIOLOGY OF THE TESTIS HORMONE.

Historical Note.—Max Neuburger,[4] following Biedl,[5] attributes the first conception of the internal secretion of the testis to the French physician, Theophile de Bordeu (1722-1776). Later writers (one of them spells the poor scientist's name like that of the well-known American maker of condensed milk) have quoted the quotation, and apparently failed to read in the original,[6] that Bordeu was merely repeating the humoral pathology of many earlier writers. He directly quotes his notion of a "reflux" of the "seminal stimulus" from the testes into the blood from Withof.[7] Bordeu further supposes with equal enthusiasm that all tissues and organs – the mucous membranes, salivary glands, mammary glands, bladder, pancreas have "refluxes" into the blood. He adds, in speaking of the "reflux" of the breasts, that he has seen "plusieurs fois des amas de fromage et de lait aigri sous l'épiderme des femmes en couche."

Marshall[8] traces the scientific growth of the conception in the works of Berthold (1849), Claude Bernard, and Brown-Séquard (1889). It has been already noted that Bouin and Ancel (1903) first suggested the interstitial cells of the testis as the source of the hormone.

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[1] Sisson: Anatomy of the Domestic Animals, Philadelphia, Saunders, 1914.

[2] Loc. cit.,p. 268.

[3] Anomalies du Testicule, Baillière, Paris, 1869.

[4] Wien. klin. Wchnschr., 1911, **24**, 1367.

[5] Innere Sekretion, 1st ed., 1910.

[6] Œuvres complètes de Bordeu, Ed. Richerand, Paris, 1818, **2**, 930; Analyse médicinale du sang.

[7] De Castratis Comentationes Quattuor, 1756.

[8] Lipschütz, A.: Loc. cit., Preface.

Introductory Comments.—The vague notion of former years that the sex secretion acts only by intermediation of the nervous system is little believed today. One need hardly stop to combat it. All the new studies point to the probability that the sex hormones, when released into the circulation, *act chemically in a selective way directly upon the cells, tissues and organs of the body* to produce certain characteristic reactions. This, however, by no means denies the evident fact that many sexual functions are subserved by reflexes of the autonomic nervous system and of the "erotized" brain.

Another remark must be made. The sex hormone in itself is not sufficient to produce complete sexual development. The thyroid, the pituitary and possibly the adrenal cortex, appear to be also necessary. What little we know of this obscure subject is discussed further in Chapter XIII.

The physiology of the testis hormone has been studied from: (1) *Effects of castration,* (2) *results of grafting experiments* and (3) *clinical phenomena in elderly men* after the climacteric.

1. **Effects of Castration.**—The results in man of ritual, accidental, punitive and surgical castration have been a matter of common knowledge almost since the dawn of history. Castration of the domestic animals—bulls, horses, sheep, dogs, fowls—is an industrial operation producing well-known effects. Experimental castration, complete and partial, of laboratory animals has supplied many physiological details. When properly done the operation is easily recovered from and involves no danger to life. If it be rudely performed death frequently ensues from sepsis, hemorrhage or gangrene; but these are complications.

A brief historical note may not be out of place, as throwing helpful light on the physiology of eunuchism, and the mentality of the victims.[1]

Ritual Eunuchism.—The Skoptsi, or Skoptsy (Russian, *skopets,* eunuch) are a secret religious sect who have existed in Russia for more than a century and a half past. In 1771 they already constituted a large body. They taught that purity of life was to be obtained only by mutilation (Matt. xix, 12; v, 28–30). They allowed marriage and the birth of one child before the operation was performed. The women were at one time required only to amputate or mutilate the breasts, but sometimes an oöphorectomy was done.[1] They hold their own today in Russian, and have also colonized in Rumania. Latterly many of them emphasize only purity of life, and do not insist on castration. The castrated portion of the sect are described as enormously fat.

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[1] The derivation of the word eunuch, from *ευνή*, *bed*, and ἔχειν, *hold* or *guard*, is said to be entirely conjectural.

The passage of Scripture just quoted (Matt. xix, 12) stirred some early Christian ascetics[2] to the formation of a sect of eunuchs. The example of Origen[3] was quoted for centuries, and if we may so interpret the note of Sir Thomas Browne:[4] "Be chaste in thy flaming days, when Alexander dared not trust his eyes upon the fair sisters of Darius, and when many think there is no other way but Origen's," was still sometimes imitated in the seventeenth century.

Punitive Castration.—This was by no means unknown in former centuries. It is to be found mentioned as a recognized punishment in the code of Alfred the Great for slaves guilty of certain misdemeanors. Its not uncommon use for private vengeance is illustrated by the famous story of Abelard.

The eunuchs of oriental countries, of Greece and classic Rome, were generally slaves castrated to increase their value in the slave markets as guardians of women. The trade of castrating slave boys for Moslem harems has continued into modern times. The mortality of the rude operation usually done was high, and prices were three or four times as high as for ordinary slaves. The century-long practice of castrating boys to retain their soprano voices in adult years for the music of the Sistine Chapel at Rome was disapproved by Gregory XIV, but not finally stopped until the accession of Leo XIII. Up to the end of the nineteenth century "castrati" sang soprano parts in the Italian opera houses.[5]

Influence of Castration on the Mind of Men and Animals.—That eunuchs are deficient in courage, or lacking in intellectual vigor, is amply refuted by the study of history. Justinian's famous general, Narses, was an eunuch. Lucian tells of Hermias the eunuch to whose *manes* even the great Aristotle offered sacrifices.[1] A negro eunuch, apparently of the Mohammedan faith, Kāfūr al-Ikhshīdī, reigned over Egypt and Syria in the tenth century, A.D., and prayers were offered for him even at Mecca. Eunuchs often had great capacity for public affairs, and under the later Roman emperors were well known in public life.

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[1] Pittard, E.: l'Anthropologie, 1903, **14**, 463. Pelican, E.: Gerichtlich-medizinische Untersuchungen über das Skopzentum in Russland, Giessen, 1876.

[2] *Valesians.* St. Augustine (Opera Omnia, Paris, J. P. Migne, 1831, Tom. **8**, col. 32) remarks of them, "Valesii et seipsos castrant et hospites suos." This seems all that was known of them.

[3] Neander: History of the Christian Religion and Church, Torrey's translation, London, Bohn, 1851, **2**, 462.

[4] Christian Morals, I, III.

[5] Arts., Eunuch and Eunuch (Muslim) in Encyclopedia of Religion and Ethics, Edinburgh, Clark, 1912, with copious references; also Arts., Eunuch and Skoptsi, Encyclopædia Britannica, 11th ed., with references.

In view of the contempt, ridicule and persecution which have always followed after the physically deformed, it is not to be wondered at if they were sometimes haughty, or slavish, or dishonest, or revengeful. Under the Mohammedan law they could marry, but by the law of Moses they were to be excluded from the Congregation of the Lord. In India they were outcasts.

In respect of mentality, much depends upon the age at which castration is performed. Surgical castration in middle age is apt to be followed by loss of energy and mental vigor, but there is no distinct loss of mental capacity. The occasional development of various types of mental disease after castration in middle age cannot, I think, in any case be attributed primarily to lack of the sex hormone, though its absence may reënforce a predisposition, and the administration of extract may hasten cure.

Mentality in male animals is definitely influenced by castration before puberty, but mainly only in such traits (pugnacity, courage) as go to the protection of the females of the species and the subjugation of the other males. One need only allude to the familiar mental differences between the stallion and gelding, bull and bullock, cock and capon.

Bodily Effects of Castration.—In man and animals castrated in early years (before puberty) there is a characteristic train of results. Animals grow taller, the fat thickens and the weight increases. The ox is larger than the bull, the capon than the cock. In capons the crow is abortive, male plumage fails to develop, and spurs, comb, and wattles are deficient. In castrated roe-deer the horns fail to grow. Prepuberal castration of boys is followed by unusual growth of the long bones; pubic hair is deficient; the beard is scanty or absent; the fat is increased; the larynx tends to retain its childish shape and size. Eunuchs are, therefore, apt to be tall men, with high-pitched voices.

A curious allusion to some of these facts, apparently supposed to be familiar to his readers, is made by Chaucer (Complete

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[1] Encyclopædia Britannica, loc. cit.

Poetical Works, W. W. Skeat's edition), in his description of the Pardoner, in the Prologue of the Canterbury Tales:

> "A voys (voice) he hadde as small as hath a goot (goat).
> No berd hadde he, ne ever sholde have,
> As smothe it was as it were late y-shave;
> I trow he were a gelding or a mare."

It is usually stated that in both man and animals castration is followed by an *enlargement of the pituitary gland.* The pituitary of bullocks, so far as I have observed, is not materially larger than that of bulls and cows. A. Marrassini[1] discusses the previous literature, reports some indecisive original studies of cattle, sheep and fowls, and concludes that individual variations are very great, and the cases studied too few to justify so sweeping a conclusion. One must also bear in mind that castration profoundly modifies the general somatic metabolism, and that the sum total of energy, being relieved of the work of sexual differentiation, might readily produce increase in size of all the organs as it does in the production of fat and the growth of the bones. As far as my knowledge of the literature goes, a large number of carefully controlled estimates of all the organs in castrated and normal animals has not been made. One or two glands cannot be studied alone. (See also Thymus, p. 327.)

Tandler and Gross[2] have reported some careful studies, and a complete autopsy[3] on a negro eunuch from Zanzibar. The same authors[4] have recorded some accurate observations on the anatomical characters of certain Skoptsi. In one such person, aged thirty-five years, the epiphyseal junction in one long bone was still to be seen in roentgen-ray photographs. Pittard[5] gives numerous measurements.

Probably the most noticeable bodily result of castration is *increase in fat.* Lipschütz[6] noted an amount of abdominal fat in castrated rabbits that was fully 10 per cent of the body weight, as against 3 per cent in normal males. I do not know of any recent metabolism studies on castrates. Whether or not the increase in fat is intermediated by the thyroid or the pituitary is entirely conjectural.

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[1] Arch. ital. de biol., 1910, **53**, 419.

[2] Wien. klin. Wchnschr., 1907, **20**, 1596.

[3] Arch. f. Entwickelungsmech. d. Org., 1909, **27**, 35.

[4] Biologische Grundlagen d. secundären Geschlechtscharactere, Berlin, Springer, 1913; Arch. f. Entwickelungsmech. d. Org., 1910, **30**, 236.

[5] Loc. cit., p. 275.

[6] Loc. cit.

Sex Organs.—Castration after adult years is not always immediately followed by either lack of desire or *impotentia coëundi*. This fact is occasionally verified in clinical experience with men, and by the observations of veterinary surgeons on bulls and horses. In man the nervous and mental reactions probably have something to do with the preservation of reflexes normally established prior to castration. Juvenal alludes to the employment of eunuchs by voluptuous Roman ladies of the later Empire to avoid the inconvenience of possible conception and abortion.

Prepuberal castration has effects that vary with the length of time (before puberty) at which the operation was done. Done upon small boys castration generally abrogates sexual desire and potency, and may be followed by more or less atrophy of the genitalia.

The effects of postpuberal castration on the secondary sex marks of men are not well authenticated. I find among old authors the statement that the voice becomes piping. It seems better established that the beard stops growing, and may even fall out. S. Voronoff[1] mentions that in a eunuchoid Syrian in whom he grafted a monkey gland the beard began again to grow, and that in a "rejuvenated" elderly Englishman the bald calvarium became covered with "hairs 3 cm. long."

Prepuberal castration of laboratory animals at various ages has been intensively studied by Steinach in rats, by A. Lipschütz in guinea-pigs, by Richon and Jeandelise in rabbits. For references the list of Lipschütz[2] may be consulted. There can be no question that prepuberal castration in these animals is followed by retention of the infantile, undifferentiated shape of the pelvic bones and the infantile size of the penis, prostate and seminal vesicles. In prepuberally castrated females heat fails to appear. The psychosexual behavior of such animals is entirely different from the normal for each sex. There is no virilism in the females, nor feminism in the males, but an indifferent or neutral state.

2. **Grafting of Sex Glands.**—By grafting of sex glands it may be proved beyond question that they produce a specific sex hormone. Without going into the history of the subject, which was attended by many early failures,[3] it can be here only briefly noted that the researches of Steinach[4] first successfully indicated that somatic and functional sex characters develop normally in castrated animals into which iso- or homoiotransplants of sex glands have been grafted.

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[1] Loc. cit., p. 347.

[2] Loc. cit., p. 267.

[3] Biedl: Loc. cit.

[4] Centralbl. f. Physiol., 1910, **24**, 551.

Penis, seminal vesicles and prostate are of normal size; copulation is normal, though the animals are of course sterile. Lipschütz has apparently proved that by various modifications of castration the sex development of males can be retarded, but finally completed. When, as sometimes happens, the graft fails to take, the animal shows all the signs usually resulting from castration.

Studies by Pézard[1] seem to indicate that the same experiment succeeds with cocks.

In man testis grafting has been recently reviewed by Mauclaire.[2] There have been many failures, but successful cases have been reported by Lichtenstein,[3] by Stocker, by S. Voronoff and others. The question will be more fully discussed under Treatment (p. 299). Here the matter is mentioned only to correlate the fact of occasional success with the rest of the physiological data. R. T. Morris[4] thought that a testis graft in a man, aged twenty-seven years, stimulated the growth of an atrophic testis.

3. **Clinical Studies of Elderly and Old Men after The Male Climacteric.**—These studies are in general confirmatory of other scientific facts. The genital organs shrink, desire fails, and energy and initiative are diminished. Only the proper amount of emphasis, however, must be laid on these signs as causally connected with the sex hormone, for the processes of senile decay are general. Arteriosclerosis, white hairs, trembling muscles and stooped frame, with complete lapse into the life of habit, are not signs of sex failure so much as of somatic breakdown.

This array of facts, observations and experiments is quite sufficient to prove that the testis produces a specific hormone, by which the male characters of man and animals are developed and perfected. In a later section of the chapter some evidence will be given to show that this hormone is *sex-specific.* (Lipschütz.)

ANATOMY OF THE OVARIES.

The ovaries, like the testes, have a double function, ovulation and hormone formation. They are two in number, and are suspended in the female pelvis upon the rear surface of the broad ligaments, behind and below the Fallopian tubes. They are ovoid bodies, flattened from above down, whitish in color, with a smooth or puckered surface. They are about 4 by 2 by 1 cm. in size. The anterior straight border is attached to the broad ligament; the rest of the organ is free, and is covered with a single layer of columnar epithelium, the *germ cells.*

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[1] Bulletin biol. d. l. France et d. l. Belgique, 1918, **52**, 91.

[2] Arch. d. mal. d. reins et d. org. génito-urinaires, 1923, **1**, 513.

[3] Wien. klin. Wchnschr., 1918, p. 1217.

[4] Jour. Am. Med. Assn., September 2, 1916.

Histology.—Upon microscopical examination the cut surface (Fig. 48) shows vessels, spindle-shaped cells, ordinary connective tissue, and many round transparent vesicles or follicles called *Graafian follicles.* Each Graafian follicle contains an *ovum*, and is lined by a layer of cells called the *membrana granulosa*, which is contained in a connective tissue capsule called the *theca interna.* The ova have been observed to originate from the ingrowing cells of the primitive germ epithelium which are gradually enveloped by a capsule from the ovarian stroma. During sex life one or more of the follicles enlarges from time to time, bursts its capsule and discharges an ovum, which enters the Fallopian tube, and is thence conveyed to the uterus. In the unimpregnated female the burst capsule heals slowly with a temporary growth of yellow cells in its interior (*false corpus luteum*). In the impregnated female the burst capsule, on the contrary, develops into a well-marked yellow body occupying a large portion of the ovary, and called the *corpus luteum verum* or corpus luteum of pregnancy (Fig. 49). Sections of the corpus luteum show it to contain a reddish nucleus of organizing or organized clot. The tissue itself is made up of large rounded yellowish cells with vesicular nuclei called *lutein cells.*

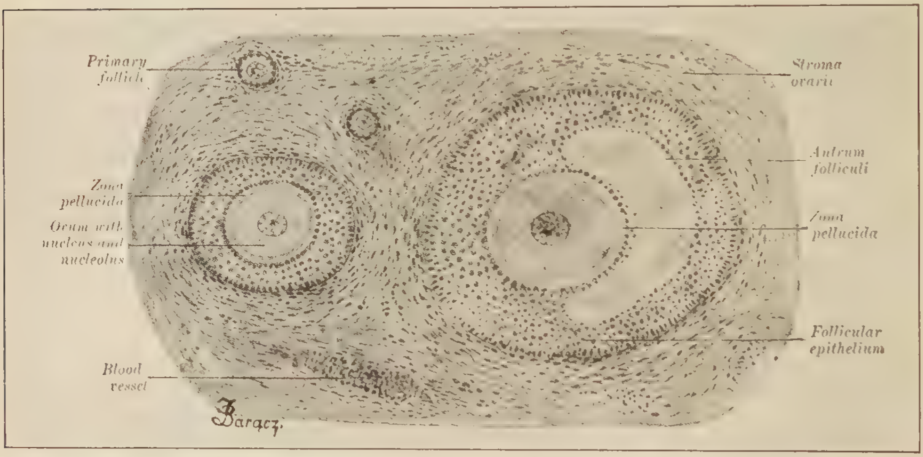

FIG. 48.—Section through cortex of ape's ovary. × 150. (Szymonowicz.)

Nervous and Vascular Supply.—The vascular supply of the ovaries is derived directly from the aorta by way of the ovarian artery.

The nerves of the ovaries are from the sympathetic and parasympathetic nerves.

Supernumerary Ovaries.—Supernumerary ovaries appear to be exceedingly rare. By Mauclaire and Eisenberg-Paperin[1] fifty-two more or less authentic cases were collected from the literature since 1864. Smith and Wood[2] reported a case.

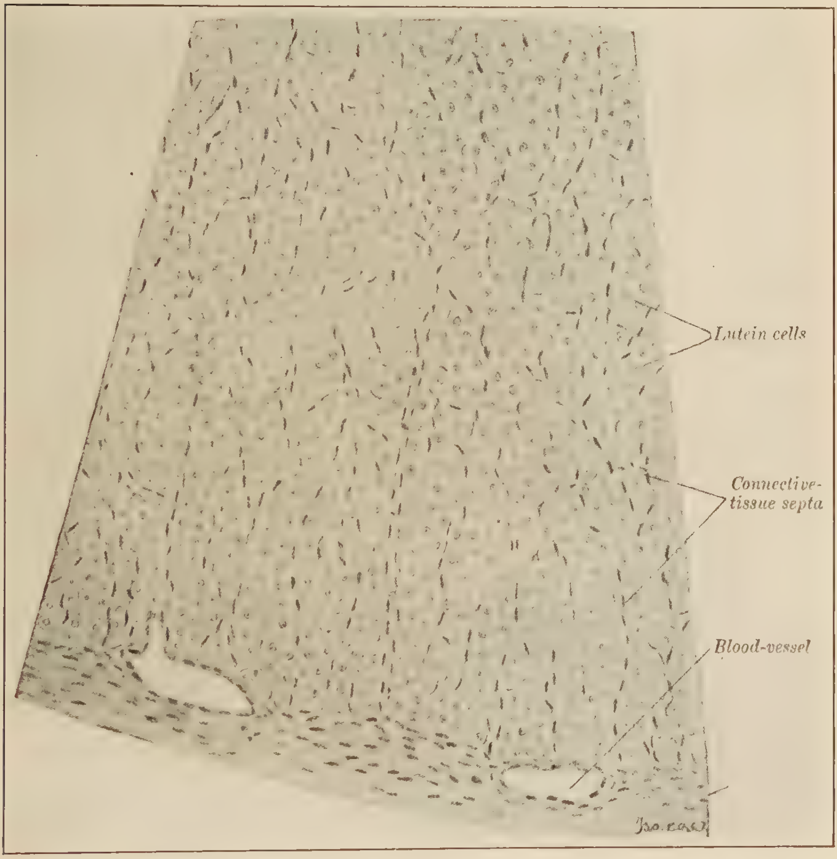

FIG. 49.—Corpus luteum of bitch. × 300. (Szymonowicz.)

Embryology.—For the embryology of the ovaries the note on the embryology of the testes may be consulted.

Cellular Source of the Ovarian Hormone.—Starting with a general admission that the influence of the ovary upon the female organism is primarily chemical or hormonic, one cannot advance even a step further without entering a field of animated controversy. The cellular origin of the hormone is a matter of dispute. The chemical unity or diversity of the hormonic influence is also disputed. It seems impossible to deny that the corpus luteum of pregnancy provides hormonic material of a specific and indispensable character during gestation; but while pregnant rabbits abort after oöphorectomy, pregnant women have been found to go on to term.[1] Marshall[2] thinks it "legitimate to suppose" that a small fragment of ovary escaped removal in these cases. The source of the chemical influences determining the onset of puberty, the recurrent cycle of menstruation and the beginning of lactation are also obscure. The immense literature of the subject is reviewed by many authors. A. Lipschütz[3] and F. H. A. Marshall[4] may be referred to for a modern account of the subject. Only a few points may be considered here.

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[1] Arch. gén. d. chir., 1911, **5**, 755. [2] New York Med. Jour., 1916, **104**, 835.

The histological appearances of the ovary are much more complex than those of the male gonad. Besides the cells of the stroma there are the cells of the atrophic follicles to be considered, the cells of the theca, of the membrana granulosa, of the normal follicles, and also, as we have already mentioned, the corpus luteum cells. Moreover, the microscopical appearances of the ovary in various mammals are perplexingly different. The results of roentgen-ray exposures are conflicting. The appearances of grafted ovaries are also confusing, for, unlike the testis, fragments of grafted ovary increase remarkably in size, and the array of different kinds of cells is as great as ever.

Marshall and Wood[5] suggest that the interstitial cells, the ripening follicles and the corpus luteum produce chemically different hormones, the first maintaining the normal nutrition of the uterus, the second evoking heat and the third subserving the uterine and mammary hypertrophy of pregnancy.

Lipschütz[6] inclines to the view that there is only one hormone; that it derives in part from the cells of the membrana granulosa, in part from the cells of the theca interna, and that these cells originate from atrophic or from normally ripening follicles.

Edgar Allen and numerous coworkers[7] have made some extensive and interesting chemical and physiological studies of the liquor folliculi, corpus luteum, placenta, and whole ovary. All this work awaits development and confirmation.

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[1] Bell, Blair: The Sex Complex, London, Baillière, 1920.

[2] Physiology of Reproduction, 2d ed., London, Longmans, 1922.

[3] Loc. cit.

[4] Loc. cit.

[5] Jour. Physiol., 1923–1924, **58**, 74.

[6] Loc. cit., p. 270.

[7] Jour. Biol. Chem., 1924, **61**, 711; Am. Jour. Anat., 1924–1925, **34**, 133, references.

PHYSIOLOGY OF THE OVARIAN HORMONE.

The internal secretion of the ovary has been studied from the results of experimental and surgical oöphorectomy (human and mammalian), from ovarian grafting, and from clinical phenomena of ovarian disease in woman, and of the female climacteric.

Prepuberal Oöphorectomy.—In the case of girls exact scientific data are very scanty. Religious history records a few cases in which it was done for ritual purposes; but the difficulty of doing an oöphorectomy without fatal hemorrhage and peritonitis by the rude surgical methods of ancient times was an automatic bar to survival. A few instances of the practice among savage tribes have been recorded. Experimental prepuberal oöphorectomy in female mammals and birds (called industrially *spaying*) causes, *mutatis mutandis*, the same bodily results as in males; growth is continued; the long bones are longer; the fat is increased; the genital organs remain infantile; menstruation and heat fail to appear, and pregnancy is impossible. In a small girl the operation may be expected to check or arrest the growth of pubic and axillary hair, the breasts will be infantile and sexual desire will be abolished, with its train of psycho-sexual manifestations.

In mammals and birds the occasional failure of oöphorectomy to produce this train of events is attributable to an accessory gland or an imperfect operation; residual fragments of ovary are known to hypertrophy with considerable speed. In hens the right ovary is usually atrophic; when the functioning left ovary is removed, the right can conceivably in some cases be stimulated to supply the lack.

Grafting.—Iso- and homoiotransplantation of fragments of ovary in rats, guinea-pigs and rabbits has been extensively studied.

Ribbert[1] first described the histological condition of grafts. Marshall[2] reported that in the rat the transplanted ovary may undergo normal cyclical changes, or all the follicles may finally undergo atresia. If grafting be done after prepuberal oöphorectomy, normal bodily and sexual development are continued. Partial castration is followed by hypertrophy of the fragments left behind. This question has been carefully and elaborately studied by Lipschütz,[3] who has tried to explain the difference in this regard between males and females.

Clinical Facts.—The *climacteric* in woman occurs from the fortieth to the fifth-fifth year. Some women at sixty state that they are still menstruating. Probably they have failed to recognize the difference between the menstrual nisus and the occasional bleeding caused by submucous fibroids, cervical polyps, or by the insidious onset of malignant disease. Some conceal the truth for the same reason that they conceal their ages.

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[1] Arch. f. Entwickelungsmech., 1898, **7**, 688.

[2] Trans. Royal Soc. Edinburgh, 1907, vol. **45**.

[3] Loc. cit.

The *normal climacteric* in woman is usually signalized by an irregularity of a previously normal flow, and a little later by complete cessation of the menses. There gradually develops about the the same time an increase in fat, an atrophy of the uterus and ovaries and breasts, a slight rise in blood-pressure and a greater fatiguableness. There is a gradual loss of sex appetite, or perhaps a temporary flare-up of the flames of desire, followed by permanent extinction. The pathological symptoms of the menopause will be noted in a later section of this chapter. The psycho-sexual behavior may or may not change. Sexual revulsion or aversion at and after the climacteric is not always pathological as a substitute for desire; *contrariorum eadem est scientia.*

Mental changes are to be interpreted much as in the case of men (p. 279). Those precisely due to diminution of the ovarian secretion cannot be differentiated with any great exactitude from those normally associated with the approach of old age. The most marked immediate difference is the loss of initiative and the extension of habit-life into all the operations of the mind. In extreme old age the mental reactions of men and women are removed entirely from the voluntary sphere and become automatic responses to stimuli.

It is a matter of general observation that after the climacteric the *face-hair* of women, normally only a downy growth on lip and chin, hardly visible in blondes and not remarkable in brunettes, tends to increase in length and quantity. There are frequent references to the fact in literature; Macbeth's witches on the stage are provided with mustaches and beards; Thackeray in one of his novels speaks of the "stout and bearded dowagers" to be seen in his day riding daily in Rotten Row. Just how much the ovaries, the adrenal cortex, the thyroid or the other endocrines have to do with this curious phenomenon is not at all clear. The matter will be mentioned again in the section on Hirsutism.

It is perhaps worth while to note again carefully that in healthy and normal women all these changes are very gradual. The ovarian secretion is not suddenly abolished—only slowly diminished.

After double postpuberal oöphorectomy J. Oliver[1] found that in one of his patients the menses were not suppressed. He infers from this that the ovaries are not essential the maintenance of this function. Marshall,[1] however, thinks it much more likely that such an occasional occurrence may be "due to the presence of accessory ovaries which are occasionally known to exist," or to imperfect excision of the normal glands. He offers the same explanation for the very rare cases of pregnancy reported after excision of both ovaries. All such events are so exceptional as to bring the exactness of the facts into question. In the case reported by Dannreuther[2] he thought he had reëstablished the menses, after double excision of the ovaries, through administration of corpus luteum.

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[1] Jour. Physiol., 1912, **44**, 355.

In the overwhelming majority of cases, after the removal of both ovaries, the immediate results are permanent amenorrhea, with "nervousness," and a vasomotor instability of the vessels of the skin (supposed to be due to intermittent interruption of sympathetic tone) causing "flushes." Atrophy of the mammæ, increase in bodily fat and a tendency to rise of blood-pressure slowly follow. Mental symptoms, particularly melancholia, have been observed, but one cannot, I think, in such cases consider oöphorectomy as more than a predisposing cause.

Finally the dermatologists have associated a series of skin diseases both with the artificial and the natural menopause. Here the causal relation is obscure, and far from a demonstration.

Mammary atrophy after double excision of the ovaries has been supposed to diminish the probability of the development of cancer of the female breast, and to improve the chances of recovery when such cancers are present. The operation is called from the name of the proposer,[3] "Beatson's operation." I gather from the opinion of surgical friends here in New York that it is not popular. Beatson gave thyroid after operation. R. Abbe[4] reported some cases.

SPECIFIC NATURE OF SEX HORMONES.

The specific character of the male and female sex hormones seems to be fairly well established by the facts of "cross-grafting;" and by the assumption that the male and female hormones are specifically different, one has a reasonable and satisfactory explanation of many of the facts of hermaphroditism.

Cross-grafting.—Successful cross-grafting was first announced by Steinach[5] in rats and guinea-pigs. By grafting the ovaries of young females into young castrated males, the males were feminized in many significant ways. Their growth was reduced, fat increased, quality of hair modified, and in guinea-pigs the male mammæ developed from the normal rudimentary state into well-formed large female mammæ. (This could not be observed in male rats, which have no mammæ.) Steinbach claimed further that the feminized males were pursued by normal males, and that castrated males in the same cage were unnoticed.

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[1] Loc. cit., p. 282.

[2] Loc. cit., p. 302.

[3] Beatson, G. T.: Lancet, 1896, ii, 104, 162; Brit. Med. Jour., 1899, i, 399.

[4] New York Med. Jour., August 3, 1901; Med. Record, December 14, 1901.

[5] Arch. f. Physiol., 1912, **144**, 71.

In respect of the psycho-sexual behavior of caged animals, no very reliable scientific conclusions may be drawn, for in all animal laboratories it is well known that male dogs and male rabbits attempt coitus with other males and the same is said to be true of female rabbits with other females. Among unconfined domestic animals, like cows, the same spectacle may be daily noticed in any pasture field or cow-yard. But the other facts noted by Steinach are of some significance, and experiments by later writers have confirmed them in many ways. Athias[1] found that in the castrated and ovary-grafted male guinea-pig the mammæ enlarged greatly, and contained abundant milk. The studies of Moore[2] and of Lipschütz[3] are also confirmatory. Primary failures and early secondary recurrences to the "castrate" state occurred, but in such cases the graft had failed to grow, or grew only for a time.

Cross-grafting experiments upon hens (Pézard, Goodale and Zawadowski) have been reported as successful. Details and references may be found in the volumes by Biedl and Lipschütz. In one of Zawadowski's[4] grafted hens it is said that "The comb began to grow ten days after the operation. The general behavior was that of a male. The masculinized hen spreads out the tail and wings, follows the hens with rapidity and great persistence, offers them food with a truly masculine gallantry, and crows with a clear well-developed male voice."

Hermaphroditism.—The term is derived from the name of an ancient Greek divinity, Hermaphroditus, who was said to be partly male, partly female. This sex duality was also attributed to Dionysus, and Priapus—a union in one god of the two great principles of generation and conception. The myth probably originated in the Orient. Ovid's story[5] is a later Hellenistic legend which derived from a mistaken etymology.[6] In the prurient conversation of the illiterate vulgar in the United States the word is familiar in the corrupted form "morphidite." R. Goldschmidt[7] has used as a synonym the word *intersexuality*.

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[1] Compt. rend. soc. d. biol., 1915, **78**, 410.

[2] Jour. Exp. Zoöl., 1919, **28**, 137.

[3] Loc. cit.

[4] Quoted from Lipschütz (Russian original not seen).

[5] Metamorph., **4**, 285.

[6] Art., Hermaphroditus, Encyclopædia Britannica, 11th ed.

[7] Endocrinology, 1917, **1**, 433.

Hermaphroditism may be complete or *true*, and incomplete, when it is called *pseudohermaphroditism*. The true hermaphrodite has organs producing both ova and spermatozoa. The partial hermaphrodite has the generative organs of one sex (ovary or testis) and an abnormal development of one or more of the secondary sex marks of the other. Thus there arise a *female pseudohermaphroditism* and a *male pseudohermaphroditism*. The former is also called virilism. The latter feminism.

In a perfectly unisexual individual all the sex marks of the other sex are absent. Such an individual is purely *diœcious*. But as Marshall[1] remarks, "Among animals that are usually regarded as purely dioecious there are many instances of vestigial or even of functional sexual organs of one sex being present normally in individuals of the opposite sex. The mammary glands and teats of the male mammal and the clitoris of the female are examples of such organs." One may, therefore, regard mankind as made up normally of males and females, each of whom carries a latent or recessive tendency toward the sex qualities of the other. "Male and female characters coëxist (though they are very unequally represented) in most if not all diœcious individuals; that is to say, that such individuals are rarely, if ever, wholly male or wholly female." After sufficient acquaintance with human character every one knows that the degree to which the dominant controls the recessive sex character in men and women has very wide normal limits.

Some recent writers on *psycho-sexual inversion* (Steinach and others) have been led to the enthusiastic generalization that such phenomena are due to the combined influence upon brain and body of small aberrant rests of one sex gland present along with a relatively normal amount of the other. But psycho-sexual behavior is a very complex phenomenon. Many of the cases admit of a different explanation. Effeminate men and masculine women owe their idiosyncrasies of conduct often to a plurality of secondary causes, none of which is directly related to the sex hormones.

While of great scientific interest, hermaphroditism belongs to the curiosities of medicine, and the limits of this book, as a clinical guide for practitioners, make it impossible to give more than a few general details. For the immense literature the text-books of zoölogy and embryology should be consulted.

In plants the presence of both sex elements in one individual is the common arrangement. Such plants are *monœcious*. The stamens develop on the same receptacle that bears pistil and ovary.

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[1] Loc. cit.

In many invertebrate animals (tape-worms [Fig. 50], some molluscs, some crustaceans) each individual carries the male and female organs, and is a true hermaphrodite. In insects the sexes are separated for the most part. In birds complete intersexuality is a rare developmental anomaly; but among poultry cases have been reported in which one fowl was found to lay eggs, to tread the hens, and to crow, and at autopsy an ovario-testis was identified. Partial hermaphroditism is more common, as indicated by spurs, comb, wattles, plumage and behavior. In the lower mammals a number of cases are on record of hermaphroditism of various degrees of completeness. Possibly no case of complete hermaphroditism in mammals ever occurs (Gudernatsch). In man partial hermaphroditism is seen from time to time, and the cases have been collected, studied with great diligence, and variously classified. A typical illustrative case has been reported by W. Blair Bell.[1] The patient menstruated at fourteen years, stopped again at fifteen and a half years. She was first seen at seventeen years of age for amenorrhea. Her voice had gotten deeper at that time, but she looked like a normal girl. The abdomen and rectum were negative. Two years later she had grown a small mustache, her legs and trunk were covered

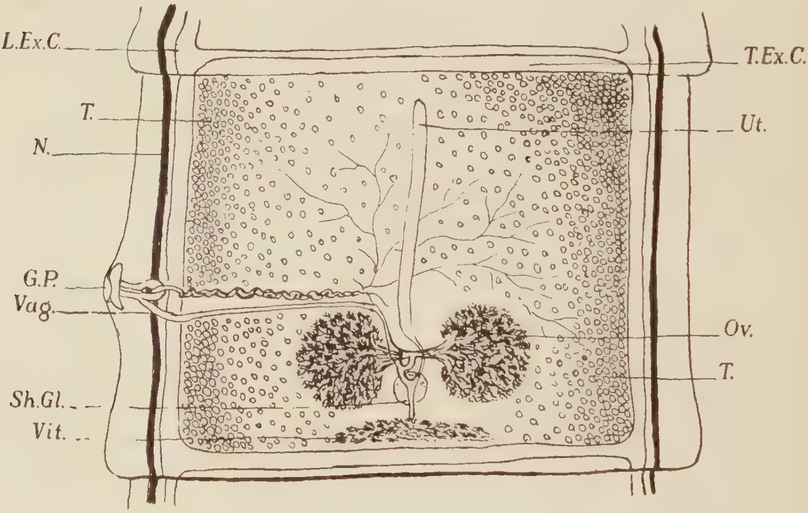

Fig. 50.—Proglottis of Tænia saginata (Goeze), showing genitalia. *L.Ex.C.*, left excretory canal; *T.Ex.C.*, transverse excretory canal; *Ut.*, uterus; *T.*, testis; *N.*, nerve; *G.P.*, genital pore; *Vag.*, vagina; *Ov.*, ovary; *Sh.Gl.*, shell glands; *Vit.*, vitellarium; *T.*, testis. 10/1. (From Fantham, Stephens and Theobald: Animal Parasites in Man.)

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[1] Loc. cit.

with hair, she had a clitoris 2 inches long and a well-marked prepuce. At operation the right ovary was found normal; the left was occupied by a tumor which on microscopical examination was found to be partly ovary, as generally agreed, partly an anomalous mass of tubules and connective tissue thought to be testis, the organ being therefore an ovi-testis, or ovario-testis. Removal of this mass and of the normal ovary was followed by reversion to a feminine or neutral type.

Neugebauer's immense volume of 750 pages[1] gives an historical account, an embryological interpretation and an encyclopedic clinical abstract of cases, making the attempt to cover all the literature to his date.

H. E. Jordan[2] gives an interesting review of human hermaphroditism with recent references.

Lipschütz[3] has suggested a classification of the cases in mammals, based upon the clinical appearances and probabilities. He assumes with fair reasonableness that intersexuality is due to formation in one individuality of both sex hormones, which may act successively, simultaneously or alternately, and for a short time or a long one. There are many other classifications.

Besides the cases of fortuitous origin among mammals, there have been a few cases of successful *experimental hermaphroditism*. Steinach[4] reviewed previous doubtful experiments, and reported a few of his own which seem in many ways convincing. Confirmatory experiments have followed. The supposed antagonism between the male and female gonads was confirmed to a certain extent by the difficulty Steinach found in making testis grow in females and *vice versa*. He tried to evade this trouble by castrating his animals first, and making the double graft later, the neutral state of the castrate being thought more favorable to a take.

The sex hormones are possibly not the only ones associated with intersexuality. K. Krabbe[5] has collected from medical literature 17 cases of adrenal tumor (thought to be cortical) in children. In the boys, 4 in number, there appeared to be merely a precocious puberty. In many of the girls there was hypertrichosis (beard, increased pubic, axillary and body hair), a deep voice and a hypertrophy of the clitoris. After mentioning the accepted theory that these cases (along with other similar reported cases in grown women with tumor of the adrenal cortex) are usually regarded as feminine pseudohermaphroditism, or virilism, due to excessive secretion of the adrenal tumor, he offers the opposing view that such tumors are really tumors arising from testis rests in the adrenals or the neighborhood, and retaining their normal secretory character.

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[1] Hermaphroditismus beim Menschen, Leipzig, 1908.

[2] Am. Jour. Anat., 1922–1923, **31**, 27.

[3] Loc. cit.

[4] Arch. f. Entwickelungsmech., 1916, **42**, 307.

[5] New York Med. Jour., July 6, 1921, with references.

The data are evidently quite insufficient to decide so difficult a question. Microscopical reports on the tumors were sometimes not made; in some of the cases the tumor was not even certainly identified as coming from the adrenal cortex or from an aberrant adrenal rest; and of the microscopical examinations actually made nothing suggests definitely that testis tissue was present. Jump, Beates and Babcock[1] give other theories. E. Mathias[2] has also recently reviewed the subject, with references, and a report of two new cases.

SEXUAL PRECOCITY.

This question requires at least a short notice. Normal puberty occurs in girls in the temperate zones from the twelfth to the fifteenth year; in boys from the thirteenth to the seventeenth year. That there are marked racial differences in the time of approach of puberty has been known for centuries. Hindoo girls sometimes menstruate at nine years. Mahomet's favorite wife was taken when she was nine years of age.[3] The onset of puberty is also influenced by climate, by hygienic surroundings, by psychical stimulation. The subject of early puberty was carefully written up years ago; the paper by R. P. Harris[4] is still valuable. Harris noted that while male precocity is apt to be associated with feeblemindedness and epilepsy, seemingly normal girls have been known to menstruate at one year, and by three or four years to have a large body, *crines pubis et axillarum*, rounded breasts and the physical appearance of a woman. Harris quotes from older writers a first motherhood in an English girl, a little over nine years of age, whose baby weighed 7 pounds; and in an American girl, aged ten years, whose baby weighed $7\frac{3}{4}$ pounds. The mentality of these overgrown girls was not precocious, but neither was it deficient. Lipschütz[5] gives an extensive bibliography on the entire subject in girls and boys.

The problematic relations of the pineal gland to precocious puberty are discussed in Chapter X, and the relations of the adrenal cortex to the same phenomenon have been mentioned in the preceding section of this chapter.

It is fairly well established that tumors—generally teratomata—of the ovary and testis, occurring in childhood, may be associated with precocious puberty. The explanation generally accepted is that sexual development is accelerated by excess of gonad hormone.

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[1] Loc. cit., p. 230.

[2] Virchow's Archiv, 1922, **236**, 424.

[3] Irving, Washington: Life of Mahomet.

[4] Am. Jour. Obst., 1870, **3**, 611.

[5] Loc. cit.

Finally, whether excessive secretion of the anterior pituitary gland can cause precocious puberty or not is in doubt. Accepting for the time the common view that pituitary causes growth of the long bones and concomitant development of the soft tissues, it is not always so clear from the clinical facts that precocious puberty must accompany the other signs of hyperpituitary activity. Yet deficiency of pituitary secretion causes sexual involution. Krabbe[1] also states that continued administration of pituitrin causes hypertrichosis. As far as my own experience with adolescent giants goes, puberty has appeared at the usual time.

Delayed Puberty, or Eunuchoidism.—Delayed puberty may be explained generally on the basis of the general principles already laid down. Lack of space prevents further discussion of the matter here.

HAIR AND PIGMENT.

Hirsutism, Hypertrichosis, and the Reverse.—The normal sexual distribution of hair has been noted on page 267. The not uncommon growth of mustache and beard in old women has also been mentioned (p. 284). This is curiously paralleled by the development of male feathers in old hens. The endocrine relations of this phenomenon have been much discussed. No conclusion has been arrived at. Hypersecretion of the adrenal cortex is the popularly accepted cause. The "bearded ladies" in circuses are usually instances of partial intersexuality, and require no further notice.

The occasional occurrence of an excessive growth of hair over the entire body is probably not of endocrine origin, but a developmental reversion or anomaly. It is not more difficult to explain than congenital absence of body hair. It is more common in man, but also appears in woman. The condition has been familiar since the time of the biblical worthy Esau, and probably long before him. The color of the body hair is uniform with that of the scalp hair. W. S. Maugham[2] has quite correctly made the "soft blonde hairs" on the arms of his "Saxon goddess" Sally match the blue eyes and yellow scalp hair of the same charming young person. He probably sketched from life.

Many curious anomalies in the distribution of hair and eyebrows are bravely assigned by various clinical writers to the influence of this and that ductless gland, but such statements should be labeled as pure guesses. McCarrison[3] has described a young girl with Graves's disease whose scalp hair was thin and gray. After operation on a diseased appendix the thyroid condition cleared up, all the gray hair fell out and a new and abundant growth of dark hair appeared. The reader may interpret this phenomenon in any way he pleases. The "adrenal personality" is popularly blamed for many anomalies in the distribution of cutaneous hair; but the probabilities are that most such conditions are congenital, or are local diseases unconnected or only secondarily connected with the endocrines. The reader will remember that Simmonds' disease (p. 202) is said to be accompanied by falling of the pubic and axillary hair. See also Krabbe's observation (p. 291).

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[1] Loc. cit., p. 289, no reference.

[2] Of Human Bondage.

[3] Loc. cit., p. 61.

Cutaneous Pigmentation.—Cutaneous pigmentation of various kinds accompanies Addison's disease. This is a general hypoadrenia, but the pigment signs are usually ascribed to cortical deficiency. Patches of brown pigment and of leukoderma accompany many chronic uterine diseases; whether deficiency of ovarian hormone is the cause or not is unknown. Pigmentation of the mammilla and mammillary areola deepens in pregnancy, especially in brunettes. The genitalia externa of normal men and women are deeply pigmented. Some further notes on pigmentation of the skin, diagnostically viewed, will be found under the diagnosis of Addison's disease.

PHYSIOLOGY OF ŒSTRUS.

The word *œstrus,* or *œstrum,* is directly from the Greek. It means primarily gad-fly, metaphorically the sting produced by its bite, then madness or frenzy in general, and especially the madness of sexual desire. The English synonym for females is *heat;* for males, like the stag, *rut.* The German is *Brunst.*

Breeding Season.—There is a breeding season for many mammals, the phrase covering comprehensively the period during which the physical changes in males and females preparatory to sex union, and the changes wrought in the female by coitus, conception, parturition, and lactation occur. There may be one, or, in the absence of fruitful coitus, several *œstrous cycles* during one breeding season.

In women and the female primates there is regularly an œstrous cycle once every lunar month (*menstruation*), with its physical concomitants of vaginal hemorrhage, ovulation, uterine congestion, thyroid enlargement, and swelling of the breasts. In female laboratory mammals the pituitary swells during œstrus (p. 207). In bitches œstrus occurs generally twice a year, though there are many exceptions.

The ultimate cause of this periodicity has been much discussed. In woman serious efforts have been made to associate it causally with the changes in the moon. But while climatic and seasonal changes evidently play a part, the question belongs essentially to the philosophy of evolution.

The immediate cause is to be found in chemical influences originating in the ovary and testis.

The Psycho-sexual Behavior of Mammals During Œstrus.—The psycho-sexual behavior of mammals during œstrus is characteristic. The conduct of the bull moose in rutting time is so well known as to have caused the attachment of his name to a political party once organized in this country by a celebrated ex-President. In mares the onset of heat[1] is sometimes marked by a flare-up of such intractable viciousness that the animal becomes dangerous and unworkable; veterinarians have successfully done oöphorectomy for the cure of the condition. Even in such gentle beasts as cows heat brings sometimes such madness as makes the animal jump high fences and break down ordinarily impassable barriers in order to reach the visioned proximity of the male.

In women the "biological imperative" (I owe this witty phrase to a friend who would probably prefer to remain nameless) has been the theme of song and story time out of mind. Among the thousands of literary studies of this phase of human existence many are admirable treatises on psycho-sexual physiology. The behavior of Sophia Baines in Arnold Bennett's *Old Wives' Tale,* and of Marcia Gaylord in W. D. Howells' *A Modern Instance* may be taken as careful and minutely accurate descriptions of the mental manifestations of œstrus in woman.

The Behavior of Female Animals Toward Their Offspring.—This is also attributable to the activation of hereditary instincts by the ovarian hormone. Among mammals generally and among domesticated fowls, the conduct of the mother is self-sacrificing, watchful, protective, anxious. The facial expression of mammalian mothers of all genera (cat, fox, bitch, woman, cow) when they look at their offspring has a striking similarity. The good human mother clucks to her babes exactly as the hen does to her chicks, and cleans them with tongue or saliva as the cat does her kittens. It is also an odd fact that among virgin women caring professionally as nurses or kindergartners for babies and small children a "psychic equivalent" for the hormonic ovarian influence of pregnancy and lactation often manifests itself in face, manner and bodily outline. They grow "motherly."

Upon the pathological extremes of œstrus in mankind there is no space here to enter. Rosalind lightly remarks, "Men have died from time to time, and worms have eaten them, but not for love." Yet the experience of daily life teaches that suicide, murder and various types of insanity may be often ultimately traced to the reactions upon the psyche of the sex hormones.

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[1] Marshall: Loc. cit.

Pregnancy.—There can be no question that the ovarian hormone, or hormones, plays an important part in the nutrition of the uterus, and the hypertrophy of the mammary glands during pregnancy. Many writers have supposed that the corpus luteum verum provides a hormone with special chemical adaptations. The point has been already discussed on a preceding page.

Lactation.—The relations of lactation to the ductless glands are difficult and obscure. One recent popular writer observes, "We have here an exquisite sample of the checks and compensations which make for a self-balancing of the whole endocrine system." But this author's conclusions do not appear to be based upon the facts of recent scientific literature.

Experiments in vast number have been accumulated to support various theories of lactation. The corpus luteum has been generally supposed to be the essential factor; but there are instances where after double excision of the ovaries during pregnancy normal parturition and lactation have been observed.[1] The "fetal hormone" theory was proposed by Starling and Lane-Claypole. The placenta, and certain special uterine glands, have been also supposed to produce hormones influencing the growth of the mammæ. The profuse flow of milk in woman after parturition, with the curious occasional phenomenon of "witches' milk" in the breasts of the new-born infant (whether boy or girl), has tempted the incautious affirmation that at birth an inhibition upon some milk-secreting hormone is lifted, and that the infant, when nursing, also gets the released galactagogue. But this is purely speculative. The question is complicated by the fact that virgin bitches have been known to secrete milk;[2] that virgin girls have secreted quantities of milk after allowing infants to suckle;[3] that bulls, male goats, rams and men have been known to give suck,[4] indicating, as Marshall[5] remarks, that at times "Lactation is not even a female function." For the literature Marshall's bibliography is useful.

Certain clinical facts are to be mentioned. Women as a rule do not menstruate when nursing. If conception takes place in a woman during lactation of a previous infant the supply of milk rapidly fails in content of solids, and presently dries up. The nursing infant has to be fed artificially. Among dairymen it is well known that cows castrated or "spayed" after calving give a larger supply of milk for a much longer time than normal females, and the milk is said to contain a larger per cent of butter fat (Berkowitch[1]).

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[1] Bell, W. Blair: Loc. cit.

[2] Heape: Jour. Physiol., 1906, vol. **34**.

[3] Knott, J.: Am. Med., 1907, **2**, 373.

[4] Knott: Loc. cit.

[5] Loc. cit.

Hygiene of the Sex Hormones.—Certain general facts relating to the psychophysiology of the sex hormones are of such importance to the happiness, longevity and physical perfection of individuals, and to the future of the race, that the perspective of this book seems to require a short notice.

Alexander Bain gravely remarks that the passion of sex love is "probably the most furious and elated experience of human nature." Sex love is physically conditioned upon the sex hormones, which produce, in the patter of the Freudian school, an "erotization" of the brain, cord and autonomic nervous system; that is, they are the physical causes of desire as it appears in consciousness. Leaving to the novelists, poets and psychologists the more intimate analysis of the passion, the student of the physiology of the sex hormones sees their influence beneficently pervading the body and brain of man and woman in a thousand ways. Woman, particularly, is largely under the sway of her sex hormone, and reaches perfect physical and mental development only after she has borne a child. Man is hardly less dependent. To the poet and artist of either sex love is inspiration.

To the physiologist, therefore, it appears desirable in every way that, within the reasonable limitations of public policy, normal sex relations should not be needlessly restricted; that birth control should be invoked at the will of the parents to prevent undesired conception; that venereal diseases should be treated actively, and when necessary should be segregated; and that marriage and divorce should not be legally too difficult of accomplishment.

Sex Hormones and Eugenics.—Just how closely the physiology of the sex hormones is related to eugenics it is not possible at present to say; but in a general way there can be no question that, whether the chromosomes be modified or not, healthy sex hormones influence favorably the chemical activity of the germ cells and the fluids that subserve their nutrition. A high degree of sexual ardor at the time of intercourse probably modifies favorably the growth, if not the structure, of the fertilized ovum. Shakespeare's lines from Lear are in point:

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[1] Thèse de Paris, 1908.

> "Why brand they us
> With base? with baseness? bastardy? base, base?
> Who, in the lusty stealth of nature, take
> More composition and fierce quality,
> Than doth, within a dull, stale, tired bed,
> Go to the creating a whole tribe of fops,
> Got 'tween asleep and wake?"

Walter Pater[1] also commented years ago on "the keen, puissant nature of the love child;" and Elley Key[2] has some thoughtful remarks on the same subject.

CHEMISTRY OF THE SEX HORMONES.

It is perhaps a reproach to biological chemistry that so little is actually known to-day of the number and precise chemical character of the sex hormones. They are not more exactly understood than the vitamins are.

Several excuses may be offered. The ovulation mechanism in the ovary and the semen-secreting tubules in the testicle are so intimately associated with the tissues thought to subserve hormone formation that, except in the case of the corpus luteum, separation of the two for purposes of study has been so far impossible. The recent work of Banting has triumphed over the same difficulty in the pancreas, but no one has so far proved to be very "warm on the trail" of the sex hormones. Some commercial preparations of ovary act in a clinically satisfactory way *per os* and by hypodermic injection, but proofs of the same action for testis preparations are much less complete. In order to identify an active principle it must be administered to castrated animals in doses and intervals that imitate the natural discharge of the normal gland, and especially in females this is a hard task. But little is known of the relative quantities and intervals of secretion which evoke puberty, menstruation and lactation, or the lack of which is responsible for the menopause.

The studies of Brown-Séquard were scientific, and little deserving of the ridicule which everywhere met them. But later chemical studies, while well planned, are so far incomplete, unreliable and conflicting. For details the volumes of Biedl and Lipschütz may be referred to.

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[1] The Renaissance, Art., Leonardo da Vinci.

[2] Love and Marriage, English translation by A. Chater, New York, Putnam, 1912.

Therapeutic preparations of sex glands in use to-day are noticed in a later section. The "sex-specific" (Lipschütz) character of the male and female hormones is so well recognized now that there is no ground any longer for believing that they are clinically interchangeable.

CLINICAL ABNORMALITIES OF THE GONAD HORMONES.

Sex hormones in disease are theoretically, like other internal secretions, *increased*, *diminished*, *absent*, *perverted*. Such conditions may follow organic disease, or circulatory and chemical changes in the sex glands.

Gonad Perversions.—Of chemical perversions of the sex hormones nothing is known.

Gonad Hypersecretion.—It has been already noted that some tumors of the ovary and testis in early childhood are accompanied by signs of precocious sex development. Surgical removal is indicated. If possible one or a fragment of one normal gland should be left. In some recorded cases after operation the child's condition has reverted to that normal for the age.

Satyriasis and nymphomania are often symptoms of mental disease of various kinds; their relations to the sex glands are obscure. Successful treatment depends on many factors outside of endocrinology.

Functional exaggerations of normal œstrus in otherwise normal young people are to be treated on rational principles. Bromides are a common resource. Other stock anaphrodisiacs are listed in the text-books of pharmacology. Far more helpful is the use of cold baths, plenty of physical exercise and some absorbing occupation or diversion.

Sexual excitement due to drugs that congest the bladder and urethra (camphor, cantharides and many others) is to be treated symptomatically.

Gonad Hyposecretion. A. **The Testis.**—**Causes.**—*Undescended Testis.*—Undescended testis may or may not be the cause of hyposexual activity. Where but one testis fails to descend the normal gland can function for both. Even when both glands are undescended the interstitial cells may still function. The patient is sterile, but puberty and potentia may appear at the usual time.

Congenital Anorchia.—Congenital anorchia is almost never seen. Tandler and Gross[1] after analyzing the few reported cases, affirm that no true case has ever been reported.

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[1] Loc. cit.

Primary Congenital Atrophy.—Primary congenital atrophy is sometimes seen. The glands are in the scrotum as usual, but they consist only of a soft mass of vessels and connective tissue, not larger than a pea, even in boys of ten and twelve years. If the condition be untreated the boy's growth is eunuchoid. I have seen such a condition complicating Mongolism, though boy Mongols often have normal sex organs, and Sajous[1] affirms that they may be even sexually precocious.

Secondary Atrophy.—When atrophy of the sex organs is secondary, and follows hypopituitarism or hypothyroidism, it is rational to give pituitary or thyroid gland. In childhood this line of treatment is fruitful in inverse ratio to the degree of deficiency, *i. e.*, gland therapy is much more helpful in repairing a partial than in substituting for a total deficiency. There is no reason why testis extract should not be combined with the other gland or glands at fault; but the diagnosis of pluriglandular troubles is a difficult task; treatment can often be called only empirical.

Functional Impotence.—Functional impotence in the male as a result of diabetes or of exhausting chronic inflammations, like chronic tuberculosis or cardiac disease, is to be rationally cared for only by treatment of the primary condition. Primary functional impotence due to chemical or circulatory changes in the testis itself is also possible.

Hernia, Hydrocele and *Varicocele.*—Hernia, hydrocele and varicocele, by reason of long-continued pressure, may at times cause a partial atrophy of one or both testes.

Inflammations.—Among the acute inflammations mumps of one or both testes may occur (*orchitis parotidea*). If atrophy results on both sides in prepuberal age, a eunuchoid condition may follow. Orchitis has been also seen in malaria, typhoid and smallpox. Gonorrhea of the epididymis may obstruct the ducts and cause atrophy of the spermatogonia of the testis. Sterility results from a bilateral affection, but, as a rule, the hormone is preserved. Gonorrheal orchitis is more serious. Among chronic inflammations syphilis and tuberculosis are capable of destroying one or both testes.

Tumors of the Testis.—Tumors of the testis are a difficult chapter in neoplastic diseases. They may or may not affect the hormone. If bilateral castration be needful a permanent hormone deficiency, of course, ensues.

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[1] Loc. cit., p. 338.

Male Climacteric.—The male climacteric has been already mentioned (p. 279).

Symptoms and Diagnosis.—The symptoms have been fully set out in the section on Physiology. The patient's main complaint is impotence. The diagnosis may be one of extreme difficulty, for impotence arises from many causes not connected with the testis hormone. Exclusion is the main reliance; but there will be some cases which cannot be diagnosed exactly in the present state of our knowledge.

Prognosis.—The prognosis will depend on the causes, and the available methods of treatment.

Treatment.—When the cause can be removed treatment is successful. Varicocele and hernia should be promptly operated on. Undescended testicles should be brought down as soon as practicable in boyhood. Syphilis and gonorrhea should be actively treated.

In diseases requiring double complete orchectomy the possibility of an isotransplant should always be considered, the graft coming from an undiseased or undamaged part of the tissue removed. Stocker[1] even advocates grafting back into the scrotum unaffected parts of tubercular organs. Testis-grafting in general is considered more fully in the chapter on Gland-grafting. The papers of Mauclaire and Lichtenstein were alluded to on page 279.

Vasectomy or *vasoligation* in old men is said by Steinach to cause atrophy of the sperm mechanism of the testis, but hypertrophy of the interstitial cells, with return of potency and increase in strength, vigor and cheerfulness. This operation is a storm center at the present time, with a large literature *pro* and *con.* Those opposing say that the benefits are temporary and possibly due only to suggestion, and that later results are very discouraging. In any event, as Lipschütz observes, "rejuvenation" is not the proper word for it, unless all the other senile organs can be rejuvenated at the same time. Steinach has also recommended roentgen-ray exposures of the testes as a stimulant of interstitial cells in old age. H. Benjamin[2] gives a recent account of results of this procedure.

Testis Extracts.—*Preparation and Administration.*—The difficulties of preparing testis for clinical use have been noted (p. 296). The best extract at present known is a dried powder made from fresh glands of young animals used for food. There is no definite dose. Inasmuch as there is no certainty that the extract is completely absorbed from the *primæ viæ*, 3 to 30 gr. may be safely given. One need not be afraid of causing indigestion; "lambs' fries" are a comestible. A good preparation of this kind I have found efficient after castration and in the care of eunuchoid boys. For impotence I have not found it so efficient in middle-aged men, but here the diagnosis is much more doubtful.

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[1] Correspondenzbl. d. Schweiz. Aertze, 1916, **46**, 193.

[2] Med. Jour. and Record, December 17, 1924.

For hypodermic use alkaline saline aqueous extracts, alcoholic extracts (lipoids) and nucleoproteid precipitates have been used. Berkefeld filtration should be, of course, carefully done. Clinical results furnish the only method of standardization known at present.

I have already noted the improbability that the gonads can be used interchangeably. Some psychiatrists continue to report good results from the use of corpus luteum in certain mental derangements of men. To such statements more than the usual uncertainty of clinical reports attaches. When clinical improvement can positively be proved to occur, one must still think the effect only pharmacological.

B. The Ovary.—Causes of Hyposecretion.—These are various.

Circulatory Derangements.—Circulatory derangements in the pelvis are a possible cause. They may arise from *primary arterial disease*, from the contracting scars of *pelvic exudates* and from *displacements* of the uterus and adnexa.

Congenital Absence.—Congenital absence of the ovaries is almost unknown.

Imperforate Hymen.—If untreated an imperforate hymen results in a cystic condition of the uterus, and more or less damage to the ovaries.

Ovarian Atrophy.—For sexual infantilism and secondary sexual involution the note on similar conditions in males may be referred to.

Chronic Inflammations of the Ovary.—These are numerous, and are fully discussed in the text-books of gynecology.

Tumors of the Ovary.—Tumors of the ovary may or may not affect the hormone. Double cystic ovary may progress to the point of serious ovarian damage. Fibroid and other tumors of the uterus may compress the ovary or obstruct its blood supply.

Climacteric.—The climacteric (p. 283) is also to be mentioned, when a gradual physiological ovarian atrophy supervenes. The consequences of double oöphorectomy are mentioned elsewhere (p. 284).

Functional Ovarian Deficiencies.—Finally there are primary ovarian deficiencies which seem to be *chemical* and *circulatory*. For want of a better name we call these "functional."

Symptoms and Diagnosis.—The symptoms of the surgical conditions named occupy many pages in the surgical text-books. The signs of deficiency of the ovarian hormone have been explained under Physiology. Here it may be added that functional deficiencies of minor grade are not always easy to identify. They seem to occur not only in non-pregnant but in pregnant females. Diagnoses are too often subjective, and mistakes are common. Absence of menstruation, dysmenorrhea, bleeding, sterility, sexual frigidity *may be* hyposecretory; they are also due to a variety of local and constitutional troubles to which ovarian dysfunction is secondary. Diligent study of each case is necessary. The diagnosis can be made only by careful exclusion.

Signs of the climacteric, nervousness, vasomotor instability ("flushes"), alterations in blood-pressure, changes in weight, may begin some years before the menses stop, and persist for some years after. They should be suspected at any time after the thirty-fifth and before the sixtieth year.

I take it to be the general conservative view of the profession that mental disorders of the menopause may be aggravated by the absence of the ovarian hormone, but are rarely if ever primarily induced by it. The same is true of a rather large group of skin diseases which the dermatologists associate with the climacteric.

Treatment.—Removal of organic causes is urgent. Surgical measures of many different kinds may be indicated, ablation of tumors, correction of displacements, treatment of chronic inflammations. Double oöphorectomy should be always avoided, even in older women, except, of course, in the incidence of malignant disease. When double excision for any reason is necessary an effort should be made to leave a fragment of one ovary behind; or a bit may be sometimes saved and grafted. Such grafts sometimes take. Successful homoiotransplants have also been occasionally reported. R. T. Morris[1] mentions two. Heterotransplants never grow.

In all varieties of primary ovarian insufficiency, whether or not autoplastic grafting is impracticable, unpromising, or unsuccessful, ovarian medication is indicated. It may be of the greatest value. Its usefulness will vary, as with other glands, inversely with the degree of deficiency it is expected to supply. When all obvious gynecological troubles have been excluded, severe anemia and general wasting disease are absent, and when the age of the patient is suitable, ovarian extract may be useful in: (1) Sterility; (2) amenorrhea, dysmenorrhea and various periodic irregularities of menstruation; (3) vomiting of pregnancy; (4) primary delayed puberty; (5) the menopause; (6) after double excision of the ovaries; (7) sexual frigidity; (8) repeated abortions.[1]

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[1] Loc. cit., p. 347.

Ovarian Extracts.—*Preparation and Administration.*—Whether there be one or more than one ovarian hormone is disputed (p. 281) on scientific grounds. On clinical grounds, also, some students of the subject distinguish between corpus luteum extracts (both "spurious" and "true") and extracts of normal ovary, claiming different therapeutic results from each. The question is far from a satisfactory scientific decision. So far as my own experience goes, I have gotten the best results from a preparation which contains corpus luteum, follicle fluid and interstitial cells all together. W. T. Dannreuther[2] urges exclusive use of corpus luteum verum.

Sources of Material.—Sources of material are mainly the ovaries of pigs (sows); sometimes also of cows when these are killed for food and not condemned for tuberculosis. More than 50 per cent of pigs' glands gathered in New York abattoirs contain good-sized corpora lutea. C. P. McCord[3] concludes from a study of cows' corpus luteum gotten in Chicago abattoirs that 83 per cent of it comes from pregnant animals.

Preparations.—The desired fraction of the fresh (not frozen) glands should be minced and then dried rapidly in the cold. No fat solvent should be used. Hypodermic preparations of corpus luteum and of ordinary ovary may be had in the shops. The methods of preparation are more or less a matter of conjuncture, for no one knows now whether saline extracts, redissolved lipoids, globulins or nucleoproteids contain the largest amount of hormone. However, some of the commercial hypodermic preparations give fair results, and are valuable when the patient is vomiting. There is no very satisfactory method of standardization. Clinical results are the best guide.

Dosage.—Dosage is tentative. Commercial dried extracts *per os* may be given in amounts from 2 to 5 gr. The preparation I prefer acts in much smaller doses, especially in relieving the nervous and vascular symptoms of the climacteric. Hypodermic dosage is also tentative, but preparations containing protein will give a protein shock if given in too large amount. Large doses by mouth are said by Dannreuther[4] to cause vertigo and lower the blood-pressure, and by J. C. Hirst[5] to cause indigestion.

[1] J. C. Hirst: Am. Jour. Obs., 1918, **77**, 662.

[2] Jour. Am. Med. Assn., January 31, 1914.

[3] Ibid., April, 1914, p. 1250.

[4] Loc. cit.

[5] Loc. cit.

When vomiting of pregnancy occurs, uncomplicated by goitre or by local surgical factors or by renal incompetence, some writers prefer corpus luteum—intravenous injection of a hypodermic preparation. J. C. Hirst[1] advises that ovarian extract should always be given in this way. He has found disagreeable reactions very rare except when pregnancy was complicated by goitre. The same clinicians give plain ovarian extract for the various deficiencies unassociated with pregnancy. They usually advise discontinuance of the extract during the week in which the menstrual nisus is expected.

Success in ovarian medication depends on the accuracy of the diagnosis. Failure should not be too promptly attributed to the inertness of the drug. There can be no longer any clinical question that a properly made ovarian extract is *absorbed as such* by the stomach and bowel, and that it actually produces, or helps to produce, the specific effects that may be reasonably expected of it. Claims that after double oöphorectomy giving corpus luteum will cause return of menstruation are unconfirmed. Residual fragments of ovary may hypertrophy, thus confusing clinical inferences. Accessory glands are also possible (p. 281.)

Roentgen-ray Therapy and Diathermy.—"Rejuvenation" in elderly women has been claimed by Steinach to occur after exposure of the ovaries *secundum artem* to therapeutic doses of roentgen-rays. H. Benjamin[2] gives some details of this treatment. He speaks favorably also of diathermic treatment of the ovaries through the abdominal walls.

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[1] New York Med. Jour., 1921, **114**, 391; Jour. Am. Med. Assn., 1921, **76**, 772.

[2] Loc. cit., p. 299.

CHAPTER X.

THE PINEAL GLAND.

Synonyms.—The Latin name, *glandula pinealis* (*pinus*, fir-cone), is used in France, Spain and Italy, with flexions normal to the languages of those countries. The gland is also called *epiphysis cerebri* (by reason of its position) and *conarium* (in reference to its shape). The German name is *Zirbeldrüse,* "cone gland."

History.—The anatomists must have noticed the pineal gland many centuries ago, lying as it does so plainly in sight when the cerebral lobes are pulled aside. Sainton and Dagnan-Bouveret[1] have collected from Descartes' *Traité de l'Homme*, *Traité des Passions* and other works (written before Descartes' death in 1650, but not published until some years later), a pleasing account of that philosopher's reasons, psychological and physiological, for viewing the pineal gland, which he called *glande conarienne*, as the "seat of the soul," whence *les esprits animaux* might diffuse themselves. His writings on the subject contain numerous references to explanatory figures, which for some reason were never drawn; and after his death reverent disciples who edited and published his manuscripts constructed marvelous figures of their own design to fit his references.

By later writers, both medical and lay, Descartes' pronouncement has been repeated with mock seriousness, but never forgotten. For centuries since his day the phrase has reappeared from time to time in literature. Voltaire had great fun over it. In Walter Scott's *Fortunes of Nigel* one finds (Chapter 22) the following:

"Nigel endeavored to explain, but the idea of thieves had taken possession of the old man's pineal gland, and he kept coughing and screaming, and screaming and coughing, until the gracious Martha entered the apartment."

Up to the beginning of this century its possible function as a gland of internal secretion was entirely unsuspected, although its appearances in the lower animals were described, a few tumors of the pineal body were identified, and the dried substance of the gland was occasionally given in a purely empirical way for various diseases, such as "functional disease of the brain due to failure of nutrition, cerebral softening, chronic mania and dementia."[1] There is no information accessible to me as to how this preparation was made.

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[1] Nouvelle icon. de la Salpêtrière, 1912, **25**, 171.

Many other amusing and instructive historical matters are to be found in the histories of medicine. For pineal gland in general the bibliographies of A. Biedl[2] and K. Krabbe[3] are useful. None of them is complete, though Krabbe lists more than 300 titles. Other lists of references on special pineal subjects are noted later.

ANATOMY OF THE PINEAL GLAND.

The pineal gland is a small, reddish-gray, cone-shaped body placed just back of the posterior commissure and resting upon the two upper of the corpora quadrigemina, the nates. In some cases it is almost black from deposit of pigment. The velum interpositum envelops it. A fold of the velum holds it in place. The gland is about $\frac{1}{3}$ inch long and $\frac{1}{6}$ inch thick at its base. Its base is connected with the cerebrum by two peduncles. A finger pushed into the trihedral angle, where the two lobes of the cerebrum lie in contact with the anterior surface of the cerebellum, comes directly into contact with the pineal gland.

Histology.—The accounts in the anatomical text-books of the nineteenth century are quite inaccurate, so far as I have examined into the matter. Z. Dimitrova[4] made a comparative study of the histology of the pineal gland in various animals. She confirms the statement of Nicolas,[5] that the pineal gland of the horse contains *striated muscle fibers*, and she gives drawings of them. She never noted them elsewhere. The connective tissue was of the glia type. As to *pigment*, she found it oftenest in the horse, next often in man, least of all in bullocks and sheep. In human glands concretions were common at all ages and often thick enough to spoil the microtome knife. K. Krabbe[6] studied the microscopic structure of about 100 human pineals obtained at autopsy—ages from infancy to ninety-two years. He found no signs of degeneration in old age, though one gland (age of patient not stated) contained neuroglia only. He identified certain characteristic cells of the gland as pineal cells, and described a supporting framework of neuroglia cells and fibers. He confirmed previous observation as to patches and nodules of calcification, deposits of fat and of pigment (which he declared to be *lipochrome*), and the occasional appearance of cysts, ranging in size from that of a pin-head to that of a pea. He found no striated muscle. He mentions no relation between the age of the patient and the quantity of mineral deposit ("sand," *corpora arenacea*).

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[1] Ogle, Cyril: Trans. Path. Soc. London, 1899.

[2] Loc. cit., p. 17.

[3] Loc. cit., p. 310 (note 5.)

[4] Nevraxe, 1900–1901, vol. **2**, with references.

[5] Compt. rend. soc. de biol., 1900, **52**, 876.

[6] Nouvelle icon. de la Salpêtrière, 1911, **24**, 257, with references.

I have studied the fine structure of the pineal gland in rabbits. Sections show solid trabeculæ of roundish cells and large nuclei. The nuclei are a little larger than red blood cells and stain faintly with hemotoxylin. The connective-tissue framework is attenuated and blood-vessels are small. On its surface the flattened nuclei of its ependymal covering are seen. It looks remarkably like the parathyroids of the same animal, and has no resemblance to brain tissue. Appearances in the human infant are indicated in Fig. 51.

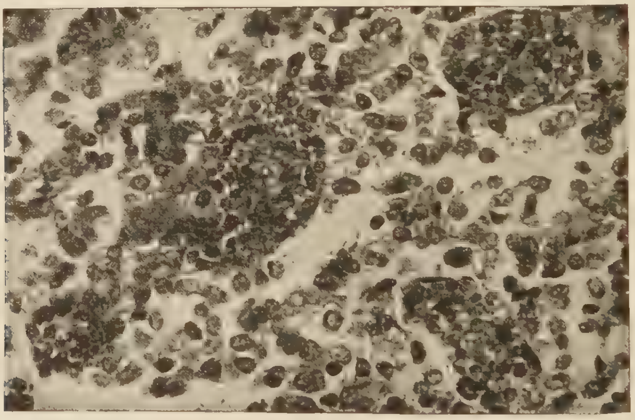

Fig. 51.—Section of the pineal of new-born child, showing loosely arranged cell trabeculæ with large blood-vessels between them. Vessels are full of blood corpuscles, which have come out dark in the photograph. × 400. (Sharpey Schaefer.)

There are some controversial points in pineal histology. F. K. Walter[1] has described and figured a number of cells with long clubbed processes which, he believes, to be specific parenchyma cells of the pineal. Krabbe has called them nerve cells and Josephy neuroglia cells.

Nerve Supply.—The nerve supply of the pineal body has not been closely studied by modern methods, so far as I am aware. The sympathetic nervous system doubtless supplies its vessels. Kolmer and Löwy[1] describe and figure a medullated *nervus conarii* in connection with the sheath of the vena magna Galeni, which they surmise to be sympathetic. Uemura[2] has also published some notes.

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[1] Ztschr. f. d. ges. Neurol. u. Psychiat., 1923, **83**, 411, with complete references.

Accessory Pineal Bodies.—Accessory pineal bodies are not mentioned in the earlier literature, to my knowledge. Kolmer and Löwy[3] mention the matter incidentally: "Wir konnten bei einzelnen Tiergattungen das Vorkommen von Nebenzirbeln erweisen;" and they describe a small body noticed in a series of sagittal sections from one "Papio" (baboon) and one puppy. The size, shape, color, reactions of the cells and the presence of pigment corresponded with the appearances in the large pineal gland.

Comparative Anatomy.—An extensive study of the comparative anatomy of the pineal gland was made by F. K. Studnička.[4] The widely advertised impression of that time, that the pineal gland is only an evolutionary vestigium of a parietal eye still observable in certain reptilia, seems never to have been more than a guess. Tilney and Warren[5] offer various reasons, based upon personal studies in the cat and in man, and upon general biological considerations, for the view that the pineal gland, far from being a vestige, follows the general lines of glandular differentiation, *is a glandular structure*, and is in some way necessary to metabolism.

Embryology.—The pineal gland is said to appear in the fourth or fifth week, arising from the neural ectoderm and getting its vessels and connective tissue from the mesoblast. F. Hochstetter,[6] somewhat modifying the view of Krabbe,[7] concluded from a study of a number of sagittal serial sections of small human embryos that the pineal anlage is first visible as a "plate" in the roof of the midbrain (Zwischenhirndach). The thickening plate makes the so-called anterior lobe of the pineal, and later the posterior lobe arises from a diverticulum of the third ventricle. The two lobes coalesce, and the diverticulum survives only as a dimple, *recessus pinealis ventriculi tertii.*

Cysts of the pineal gland may thus (Krabbe) be interpreted as snared-off rests of the pineal diverticulum, as cysts of the posterior lobe of the hypophysis are supposed to arise from the diverticulum on the floor of the third ventricle (p. 176). This view has been disputed by O. Marburg.[1]

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[1] Pflüger's Arch., 1922, **196**, 1.

[2] Loc. cit., p. 308.

[3] Loc. cit.

[4] Die Parietalorgane, Oppel's Lehrb. d. verg. micr. Anat., Jena, Fischer, 1905, with references.

[5] Am. Anat. Mem., 1919, Pt. I, with references collected to date.

[6] Anat. Anz., 1921, **54**, 193 (Ergänz.); Beitr. z. Entwickelungsges. d. mensch. Gehirns, I. Th., Deutike, Wien, 1919.

[7] Anat. Hefte, 1916, **54**, 187.

Influence of Age and Sex.—The influence of age and sex on the size of the gland has been greatly mis-stated in former years. Some recent careful work has been done by Berblinger[2] and Uemura. Berblinger weighed the pineal glands of 139 patients of various ages, from one to eighty years, and the following are the averages up to forty years:

	Average.	
Age.	Male.	Females.
1 to 10	0.110 gm.	0.164 gm.
11 to 20	0.162 gm.	0.162 gm.
21 to 30	0.166 gm.	0.158 gm.
31 to 40	0.203 gm.	0.175 gm.

Figures for later years showed a decline so that at eighty years the gland weighed little more than at ten years. Uemura's figures[3] are in the main confirmed by Berblinger's. A glance at the table will show that in girls the average weight runs a little higher than in boys, but after the twentieth year this relation is reversed. Autopsy reports indicate that the gland, if it has a secretion, is more potent in the production of tangible results (precocity) in the prepuberal period than later in life. Feeding experiments confirm this view, and rather indicate that glands from calves and young bullocks are more active in promoting growth than older animals' glands are. There is, however, no ground for the statement that the pineal atrophies at any age, or that it has any special tendency to calcification after the thirtieth year.

A. Schüller[4] in his useful text-book notes that in profile roentgen-ray photographs of the skull the pineal shadow is usually visible from about the third decade on, and sometimes even in children. The shadow is produced, of course, by mineral deposits.

PHYSIOLOGY OF THE PINEAL GLAND.

Theory and Methods of Study.—It is impossible to formulate at present a complete and consistent theory of the physiology of the pineal gland, *i. e.*, of its function in the animal body. Much of the recent literature has been written by men with only second-hand and inadequate knowledge. Misinformation is furthered also by prejudged and illogical interpretations of inadequate data by laboratory men themselves.

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[1] Loc. cit., p. 309.

[2] Virchow's Arch. f. path. Anat., 1919–1920, **227**, 38.

[3] Frankf. Ztschr. f. Path., 1917, **20**, 381.

[4] Roentgen Diagnosis of Diseases of Head, Stocking's Trans., St. Louis, Mosby, 1918, p. 156.

The known data may be arranged for convenience of study under the following heads:

Clinical and Physiological Studies.
Autopsy Reports.
Feeding Experiments and Medication.
Chemical Studies. Blood-pressure. Metabolism.
Laboratory Studies.

Clinical and Physiological Studies.—W. Timme[1] has offered evidence to prove that progressive muscular dystrophy is a disease due to insufficiency of pineal secretion. He has based his assumption upon the appearance of pineal shadows in the roentgenograms of the skull in his patients. He has described a familial group of 5 patients, 4 of whom had pineal shadows.

Majendie's ancient supposition that the pineal gland acts as a valve on the aqueduct of Sylvius, thereby regulating fluid pressure in the brain, has been modernized by Walter,[2] and Kolmer and Löwy.[3] These writers affirm the pineal gland to be a regulatory apparatus (*Regulationsapparat*) for the secretion of the liquor cerebrospinalis.

Marburg[4] has recently suggested that the pineal gland is concerned with heat regulation.

Autopsy Reports.—Attention was drawn to the secretory possibilities of the gland by Frankl v. Hochwart.[5] This eminent neurologist reported from Vienna the case of a boy, aged five years, who died of a slowly growing pineal tumor. While the child had the usual symptoms of brain tumor, he presented also a remarkable bodily growth, sexual development and mentality. This last, as evinced by several anecdotes, was far beyond his physical age. The autopsy revealed a pineal teratoma. Hochwart's report was followed by others, and the older literature was ransacked for previous reports. The symptomatology was remarkably uniform in a majority of the cases. Professor Pellizzi, of the University of Pisa, gave the "pineal syndrome" a Latin name, *macrogenitosomia præcox*. Some pineal tumors have been accompanied by adiposity only ("cerebral adiposity"), but the number of these has been much smaller. Unfortunately, signs of sexual precocity can be observed only in children under puberty. C. P. McCord[1] has laboriously collected from the literature, as far back as 1839, with references, some 90 cases of pineal tumor—25 of these in children; 23, strange to say, in boys—and summarizes by saying that too little attention was given in the older reports to the possibility of pluriglandular involvement, especially of pituitary complications.

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[1] Arch. Int. Med., 1917, **19**, 79.

[2] Loc. cit., p. 306.

[3] Loc. cit., p. 307.

[4] Arb. a. d. neurol. Institut, 1920–1922, **23**, 1.

[5] Deutsch. Ztschr. f. Nervenh., 1909, **37**, 455.

The precocity cases have been collected and discussed by numerous other writers. O. Marburg[2] reviews them again. Krabbe discusses them quite fully.[3] Many other writers have fought over them like dogs over a bone. There is no room to review the details here except to say that when all the pluriglandular, the incompletely reported, the borderline and the misinterpreted cases are ruled out, there still seems a remainder of true cases—almost all boys—in which pineal tumor was associated with sexual precocity. This is so generally agreed that the disputed cases may be omitted without damage to the argument.

Pineal Gland Absent at Autopsy.—S. Zandrén[4] has contributed an important report of a boy, aged sixteen years, a moron, who presented at autopsy no definite anatomical defect except absence of the pineal gland. K. Krabbe[5] on this point comments as follows: "Total absence of the pineal gland in man has been mentioned by some authors, but it cannot be considered as quite established, because when the brain is taken away from the cranium the pineal gland becomes oftentimes detached, as the organ remains hanging by the vena magna Galeni. . . . I was afforded the opportunity of investigating a case [of the kind] in a female infant one year old, with considerable hydrocephalus. Serial sections through the region of the pineal gland showed that the organ was converted into a sac of neuroglia with thin walls, without any sign of pineal cells. The infant presented no remarkable symptoms except its hydrocephalus, and especially no precocious puberty occurred."

Atrophy, Sclerosis and Chronic Inflammation.—Atrophy, sclerosis and chronic inflammation, as involving increase or decrease of the secretion of the gland, are to be viewed with reserve. Krabbe[6] mentions an enormous development of connective tissue in the pineal gland in a girl, aged twelve years. She died of osteomyelitis, with no other symptoms of any unusual kind. The same author[7] describes the year-long observation of a woman with chronic hydrocephalus, who was first seen as a small girl of four years, and began to menstruate at eight years. She died in middle age. Autopsy showed a pineal gland of good size, and sections were normal. The ovaries were very large.

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[1] Trans. Am. Gyn. Soc., 1917.

[2] Loc. cit., p. 309.

[3] L'encéphale, 1922, **17**, 281, 437, 496.

[4] Acta Med. Scandin., 1920–1921, vol. **54**.

[5] Endocrinology, 1923, **7**, 379.

[6] Loc. cit.

[7] L'encéphale, loc. cit.

Feeding Experiments and Medication.—It was about 1911 that Prof. C. L. Dana, of New York, first took up the subject. Dana thought it far more probable that the tumor often (the histology being variable in the different cases) might *reënforce* the gland, exaggerating the normal effect of the pineal secretion. Pineal tumors would then often act as thyroid tumors and pituitary tumors often do. With his impatience of "office-desk science," and his gift of insight which has made his influence such a power among the younger men around him, he suggested to the writer that, instead of guessing, it would be perhaps profitable to approach the subject from the laboratory viewpoint. This was the beginning of the modern period in the study of the gland.

Under Dr. Dana's constant guidance, and with some financial assistance kindly extended by the Rockefeller Institute, it was possible to report[1] in the next few years that pineal gland from calves and young bullocks accelerates the normal growth of guinea-pigs, rabbits and kittens, and stimulates the sluggish mentality of "functionally" backward children. By "functionally" backward children I mean merely those without discoverable organic defects.

About 50 of these mentally retarded children were included in the first report. Some were in the care of Dr. Goddard and Dr. Cornell, at the Vineland (N. J.) Training School; some were in the ungraded classes of the New York Public Schools; some were in the private *clientèle* of Dr. Dana and myself, and some in the care of Dr. Eleanora B. Saunders. Statistical computation of advance in mental age, checked up as far as possible against controls, was on the whole encouraging. Nurses and teachers were generally impressed with the results of the try-out. Some of the children advanced only slightly over the controls. A few did wonders. I quote the following notes on one case:

Benny W., New York (Dr. Berkeley). Weight, 42½ pounds; height, 43½ inches; age, seven years. Family history: Father not seen, reported healthy; age not ascertained. Mother, aged thirty-three years, of excellent appearance. There are three other children, all boys, aged thirteen, eleven and five years, respectively. All these were seen, and all were normal, even precocious. First visit, June 15. Personal history: Child born without accident, but was always backward. Did not walk until three years of age, and has never said any connected or intelligent words. He can repeat short sentences after his mother, but does not understand what he says. Cannot buy a penny's worth of candy. Is said to wet himself habitually, and soils himself several times a week. Mother professed herself in despair about the child and willing to do anything for his relief. Physical examination entirely negative, except that the boy is cross-eyed (150 D. hyperopic astigmatism). He has no physical stigmata, but presents a vacant animal face, smiles inanely and drools continually. His muscles and skin are relaxed, and he stands with bent knees and bowed head. He is said to be very "nervous," and cries a good deal, which might be attributable to the quantity of coffee he is allowed to drink. He was given glasses but would not wear them. The treatment of the case consisted solely in the administration of pineal gland. June 26: Weight, 43¼ pounds. Looks brighter. Mother thinks his mental condition much improved. He has gone to the toilet alone and not soiled himself all the week. He said some connected words. Cried because his younger brother was dressed before him (had never noticed this before). July 3: Mentality still improving; talks a great deal more. Weight, 41¾ pounds; a decline due possibly to the hot weather. July 10: Weight, 42 pounds; intelligence rapidly increasing; yesterday asked his mother for the key to the toilet; has entirely ceased to soil or wet himself. Height unchanged. Nurse and assistant at the clinic remarked upon the patient's improved appearance. August 14: Weight, 44¼ pounds; height, 44½ inches. Understands and answers simple questions, and has acquired between fifty and a hundred words. Facial expression transformed. Habits entirely correct.

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[1] Med. Record, 1913, **83**, 835.

A still more remarkable case is reported in the *Prescriber*:[1] A child, aged nineteen months, was the subject. The baby was unable to move its limbs or recognize its parents, lying helpless and inert on its back. No account of the physical examination is given, but thyroid had been tried and found entirely inactive. After small doses of pineal gland for three months the child was able to stand upright (supported by a chair), could reach for objects, recognized persons and seemed happy and contented.

Professor Marburg would probably not permit me to class here his case mentioned on page 323.

Sisson and Finney[2] and E. R. Hoskins[3] fed pineal gland to rats, and were unable, they said, to get any results, positive or negative. But McCord fully confirmed and amplified our observations. He used guinea-pigs, puppies, chickens and tadpoles. The controls seem to have been ample in number and variety.[1]

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[1] 1923, **17**, 368.

[2] Jour. Exper. Med., 1920, **31**, 335.

[3] Jour. Exper. Zoöl., 1916, **21**, 295.

Krabbe,[2] commenting upon the results of these feeding experiments, complains that they were not properly controlled, and that "Feeding or injection experiments cannot in the nature of things serve to elucidate the function of the organ." As to the first objection, if my own experiments be ruled out on that ground, surely McCord's were fully controlled. As to the second, while pharmacological effects of organ extracts are sometimes not such as the gland may be expected to produce *in vivo,* no one can deny that the miraculous effect of thyroid on the cretin, or of insulin in the relief of diabetic coma, is an indispensable link in the chain of evidence for the physiological identity of each of these extracts. Without similar evidence for the pineal gland the theory would be incomplete.

Chemical Studies. Blood-pressure. Metabolism.—The usual organ proteids are present, nucleoproteids, globulins and albumins. The growth-promoting principle is probably at least in part precipitated with the nucleoproteids. Dana and Berkeley[3] found that periodic intraperitoneal injections of nucleoproteid in measured amounts made subject guinea-pigs grow faster than controls. However, no great difference was noted between the action of these injections and the effect of whole gland by the mouth.

No active principle has been isolated.

The chemistry of pineal "sand" has been already mentioned (p. 305).

C. P. McCord and F. P. Allen[4] found that acetone extracts of pineal gland acted like very weak adrenalin upon the pigment cells (melanophores) of tadpoles (compare p. 170) and on strips of guinea-pig uterus. The acetone residue did not have this action but still contained the growth-promoting principle. Controls were made with muscle tissue. No mention is made of controls with cerebrospinal fluid or with brain tissues other than pineal constantly bathed in cerebrospinal fluid. The frog-bleaching effect has been confirmed by Hogben and Winton.[5]

Blood-pressure.—Dana and Berkeley found that extracts prepared in various ways had no effect on blood-pressure in dogs.

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[1] Jour. Am. Med. Assn., July 18, 1914, and 1915, **65**, 517; Trans. Am. Gynec. Soc., 1917.

[2] Loc. cit., p. 310 (note 5.)

[3] Loc. cit.

[4] Jour. Exper. Zoöl., 1917, vol. **23**.

[5] Loc. cit., p. 170.

The literature is confirmatory. For references Krabbe's account[1] may be consulted. The slight fall of pressure sometimes noted is probably not due to any special element in the pineal gland. This depressor is a general depressor found in many organ extracts and in brain tissue.[2]

Fenger[3] analyzed benzine-treated pineal glands of slaughter-house origin. He found less phosphorus and more nitrogen in glands from young animals. He makes no note of the presence or absence of iodine. Pressor effects of extracts of various kinds were negative.

Metabolism.—Dana and Berkeley,[4] in two carefully selected children, studied the total nitrogen elimination during administration of pineal gland. After a week's observation for purposes of control pineal gland was given for a week; the medication was then withdrawn and a third week's elimination was estimated. One child showed a pronounced, the other a slight, increase of total urinary nitrogen in the second week.

Laboratory Studies. – *Transplantation.*—Transplants by Exner and Boese[5] were absorbed. Young subjects were used. E. R. Hoskins and M. Hoskins[6] transplanted the anlage of the pineal from larvæ of *Rana sylvatica* into 19 other young larvæ. It failed to grow.

Excision Experiments.—This work has an important bearing on the pineal problem. Much of it has been quoted and requoted with complete neglect of the original sources, or with a superficial glance at the terminal summaries of the original papers, instead of a study of the protocols. A short sketch of this work, studied in the originals, follows, with comments:

Leo Adler[7] attempted to examine by pinealectomy the influence of the pineal gland on the development of tadpoles. The technique of his operation was apparently very defective. A frightful mortality ensued. From the dubious condition of the few surviving larvæ no conclusion whatever can be reasonably drawn.

Exner and Boese,[8] by a bloody thermocautery operation, destroyed the pineal gland in 95 young rabbits. All subjects weighing less than 700 gm. died in twelve hours. Of the whole number, 22 survived a longer time. Three males and 3 females reached sexual maturity at the usual time, no difference from the controls being observed. A cautery operation uncontrolled by the eye is of dubious efficiency, but microscopic examination after death showed, as they averred, that the pineal gland was completely destroyed.

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[1] Loc. cit.

[2] Abel: Loc. cit., p. 170.

[3] Jour. Am. Med. Assn., 1916, **67**, 1836.

[4] Loc. cit.

[5] Loc. cit., below.

[6] Anat. Record, 1919, **16**, 151.

[7] Arch. f. Entwickelungsmech., 1914, **40**, 18.

[8] Ztschr. f. Chir., 1910, **107**, 182.

U. Sarteschi[1] operated on 23 young rabbits. Three survived to sex maturity. These are said to have shown at a later autopsy remnants ("residui") of pineal gland left behind. One of them at five months was heavier than a control from the same litter by 400 gm., and had larger testes. He also removed the pineal in 15 puppies. Two survived, grew very fat and showed sexual precocity.

C. Foà[2] operated on "a series" of young rabbits—number not stated; all died. Of 63 young chicks, less than thirty days old, 15 survived pinealectomy. Of the survivors, 12 were hens and showed no change; 3 cocks had a period of depression and nutritional failure followed by a rebound in which they presently beat the controls by thirty to forty-five days in first crowing and coupling. A blank operation was done on the controls—removal of a bit of skull without pinealectomy. The same author[3] reported the same results on a second series of experiments upon 10 chicks, of which 7 survived—5 hens, no change; 2 cocks, as before. Of 8 young rats, 4 survived pinealectomy. One female showed no change; 3 males grew a little faster for a time.

W. E. Dandy[4] devised and figured a better operation. He operated on dogs and puppies. The number was not stated nor percentage ("several") of survivals. No results.

Horrax[5] operated on 82 guinea-pigs; 48 lived. There was no material change in weight in the subjects, but on the average the sexual development was slightly speeded up, with rather wide divergence between individuals. Rats were better subjects, this author thought, but his rat experiments were unfortunately ended by an epidemic.

Biedl's attempts[6] on dogs (age not stated) failed. Fearful hemorrhages were encountered. In 3 survivors of his series, living three weeks to two months, no changes were noted.

G. Christea[7] extirpated the pineal gland in 30 young cocks; 12 survived. They were much retarded in sexual development, though the body grew fairly well.

Isawa[8] did excisions on chicks. He had a terrible mortality.

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[1] Pathologica, 1913, **5**, 707, literature.

[2] Arch. ital de biol., 1912, **57**, 233.

[3] Ibid., 1914, **61**, 79.

[4] Jour. Exper. Med., 1915, **22**, 237.

[5] Arch. Int. Med., 1916, **17**, 607, references.

[6] Loc. cit.

[7] München. med. Wchnschr., 1913, p. 1051; abstracted from Rev. stiin. med. (Rumanian); original not seen.

[8] Am. Jour. Med. Sci., 1923, **166**, 185.

Only 4 chicks survived of 36 operated on. Three were males; 1 a female. Of the 3 males, 2 were depressed at first and then precocious. The backward male at autopsy was found to have a remnant of pineal left behind. The hen also had larger ovaries than the controls.

C. Zoia[1] exhibited chicks (no details) showing precocity in pinealectomized males; no effect in females.

Kolmer and Löwy[2] did a series of excisions on young rats. There were 3 rats and 2 controls in one lot, and 6 rats and 2 controls in another. The thermocautery was used, but a quick and bloodless technique claimed. The subject animals fell a little behind in weight but not significantly. Microscopic examination of the subjects at autopsy after the conclusion of the experiment showed pineals completely destroyed, and a large cerebral defect besides. Accessory pineals were searched for in serial sections of the neighboring tissues; none was found.

Influence of Castration on the Epiphysis.—The literature of this part of the subject is large, and for the sake of completeness it must be reviewed, though just exactly why the testis should react on the pineal gland because the pineal is thought to react on the testis is not clear. As a matter of fact, the experiment has been performed on a colossal scale in the beef business. All pineal gland for therapeutic and feeding purposes comes from the slaughter houses, where cows and bulls rarely appear, and bullocks are killed by the millions. No one, so far as I know, has ever found any difference in size between the pineal gland in castrated and noncastrated cattle. (See comments on pituitary after castration, p. 277.)

Biach and Hulles[3] thought that in castrated cats the pineal gland was atrophic. Sections figured are not at all convincing. U. Sarteschi[4] found that in castrated rabbits the pineal gland showed no change. Aschner[5] confirmed the conclusions of Biach and Hulles. Ruggeri[6] and Pellegrini[7] controverted them. Kolmer and Löwy[8] found castration in rats to have no effect on the epiphysis. The majority of the authors quoted are against the view that castration has any effect.

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[1] Proc. Ital. Path. Soc., Pisa, March, 1914; Centralbl. f. allg. Path. u. path. Anat., 1914, **25**, 759.

[2] Pflüger's Arch., 1922, **196**, 1.

[3] Wien. klin. Wchnschr., 1912, **25**, 373.

[4] Lavori del istituto di clinica, etc., dell'Università di Pisa, 1910, vol. **2**.

[5] Centralbl. f. Gynäk., 1913, vol. **37**.

[6] Riv. d. patol. nerv. e ment., 1914, vol. **9**.

[7] Arch. per le sci. med., 1914, vol. **38**.

[8] Loc. cit.

Critical Comment on the Physiology.—The physiology of the pineal gland has reached to-day the stage thyroid physiology had reached in 1885, or parathyroid physiology in 1900, or pituitary physiology at the time when Marie's first announcement was made of acromegaly. The theorists are as usual compassing sea and land to make one proselyte, ignoring or indignantly denying all the facts that make against their preconceived convictions; and laboratory facts and autopsy reports are contradictory in some regards, and insufficient for any positive conclusion. For another thing, in the many species of animals operated on we do not even know the percentage of occurrence of accessory pineals. Moreover, the question of metabolic rebound in young animals after injury to the brain or other organs is entirely unsettled. Premature flowering and seeding after injury to the plant is common among flowers and vegetables. Wormy apples ripen and fall long before the sound ones. In man it is perhaps an automatic readjustment for the preservation of the species that sex precocity and early fertility in idiot boys and girls in institutions is seen as often as it is. All these considerations urge the necessity of caution.

Taking up first the propositions of Timme, of Kolmer and Löwy, and of Walter, and the heat regulation theory of Marburg (see pages just preceding), one can only say that the data offered are entirely insufficient for proof of the conclusions drawn, and that (so far as I am informed) confirmation is as yet lacking.

In discussing the more generally conceded facts, it may be at once noted that the evolutionary vestige theory was never more than a guess, and the recent work of Tilney and Warren[1] has contradicted all the previous assumptions. There is then no longer any *a priori* ground for questioning the possibility that the pineal gland *may have* an internal secretion. Cowdry[2] thinks that the origin of the gland from neural ectoderm decreases the probability of its having anything to do with secretion. But the adrenal medulla is admitted to arise from neural ectoderm.

Candidly conceding the difficulties of the situation, it seems to the writer that the original assumption of O. Marburg and F. von Hochwart, reiterated with intense emphasis and conviction by the former, and with numerous "addenda" in his latest paper,[3] and generally accepted on the Continent today, is quite out of line with the facts; and that the view of C. L. Dana and the writer is still the best working hypothesis, *i. e.*, the hypothesis that best explains the majority of established data.

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[1] Loc. cit., p. 307.

[2] Barker's System.

[3] Arb. a. d. neur. Inst. 1920–1922, **23**, 1.

As regards autopsies, the evidence from pineal tumors is apparently significant. About a dozen have been more or less carefully reported in children (almost all boys) in which the tumor was associated with sexual precocity. About as many more have been reported in which precocity was absent. There is no ground for claiming (Askanazy) that the teratomatous nature of most of the positive tumors was the cause of precocity (embryonal ovarian and testis tissue being at work); for no teratoma of any other part of the brain has ever been associated with such a syndrome.[1] Let us suppose that the effect of the positive tumors lay in their production of a hyperpinealism, and that the negative tumors merely destroyed the parenchyma, producing a hypopinealism, or apinealism. This is a very simple and easy application to pineal pathology of the well-known physiological and clinical effects—sometimes plus and sometimes minus—of thyroid tumors and of pituitary tumors on the respective functions of those glands. To suppose, as von Hochwart and Marburg have done, that sexual precocity of pineal origin is due to pineal destruction (hypopinealsim), pineal secretion being supposed normally to inhibit sexual development, produces, to my mind, a confusion only comparable to the assumption of Marie, that acromegaly is due to hypopituitarism.

As regards atrophy, scleresis and absence of the gland, autopsies have shown that an extreme degree of atrophy and scleresis may exist in children without sexual precocity, and Zandrén's boy was a moron. Where hydrocephalus has been associated with sexual precocity[2] the pineal gland was in excellent condition, and the ovaries were extraordinarily large. Where hydrocephalus was associated with a fibrosed pineal in a child there were no signs of precocity. These facts fit in with the tumor data as I have proposed to explain them.

The effects of feeding the gland to young animals have been fully set out (p. 311). Sisson and Finney, and Hoskins, failed to produce any marked change in the growth rate in rats, but Dana and Berkeley, in guinea-pigs, kittens and rabbits, and McCord in a long series of well-controlled experiments on various young animals, showed that the gland hastens growth and speeds up the appearance of puberty. Also, as to medication in backward children, the results are well worthy of serious consideration.

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[1] Krabbe: Loc. cit., p. 310 (note 5).

[2] Krabbe's case (loc. cit., p. 310).

In respect of excisions, the evidence has been carefully collated in preceding pages. Biedl's, and Exner and Boese's operations were very bloody, and the mortality was so great as to call the results entirely in question. Kolmer and Löwy, Dandy, and Horrax seem to have shown pretty conclusively that the gland is not necessary to life in adult years, and that in growing rats, guinea-pigs and dogs, sexual maturity may be reached at the usual time without it. Horrax's experiments, averaged, seemed to indicate that removal of the gland may somewhat hasten sexual development, but there were wide individual differences in his animals. Kolmer and Löwy's rats were retarded a little, but this may have been due to the great severity of their operation.

Leaving these points, we have further to correlate the disconcerting results of Isawa, and the Italian observers, Foà, Zoia and Sarteschi, which are carefully summarized on page 315. Nothing is to be gained by belittling this work, which was evidently performed in a truly scientific spirit. But we must note: (1) The fearful mortality, which leaves the statistical probabilities very much against the representativeness of the survivors; (2) the initial depression of the operated cocks, followed by a rebound (metabolic rebound? accessory pineals?); (3) the failure of the hens to respond to the operation at all; (4) the entirely contradictory results of Christea on cocks, and of all the other observers on dogs, guinea-pigs, and rats. In fairness the conclusion must of course be provisional; further work may be less open to exception; but for the time operative excision can be said to show only that the pineal gland is unessential to life.

The studies on the effects of castration require no further comment.

Some writers allege that pineal tumors act only by pressure on some hypothetical sympathetic nerve center in the neighborhood. But why should 50 per cent of them fail to press? Why should 100 per cent of other brain tumors fail to press?

Some affirm that the pineal tumor merely compresses the hypophysis. This may explain cerebral adiposity, but fails to explain the typical pineal syndrome.

Again it is alleged that the pineal gland is of no value in the economy of the body because the body can do without it. But the body can do without even such important organs as the ovaries and testes, and later prepuberal castration may only slightly cripple the development of the sex organs for a number of years (Chapter IX).

The question of sexual precocity is one of great difficulty. It seems to come about in several different ways. Overgrowth of the gonads, and even (in man) of the adrenal cortex may be a cause, or a part of the cause (Chapter IX). Teratoma of the testis and ovary seems to be conceded as the commonest cause of gonad hypersecretion; if a gonad teratoma can produce a plus reaction in the sex glands, why cannot a pineal teratoma do as much for the pineal gland?

As a *provisional conclusion* I shall reaffirm that the pineal gland is a gland of internal secretion; that in childhood and adolescence its secretion promotes mental, bodily and sexual precocity; that it is not essential to life at any age, but that it probably has some useful metabolic function throughout life.

It bleaches the skin of frogs, acting *like* epinephrine, and *unlike* pituitrin, in this regard.

The interglandular relations of the pineal gland will be found discussed in Chapter XIII.

DISEASES OF THE PINEAL GLAND. ADMINISTRATION. DOSAGE.

We will consider the diseases of the gland under the heads of *tumors* and *degenerations, inflammations, secretory derangements.*

TUMORS AND INFLAMMATIONS OF THE PINEAL GLAND.

Tumors.—In respect of tumors there is not much to add to the details already given. Pineal tumors are rare. The literature contains reports of perhaps a round hundred. Syphiloma, tubercle and cellular tumors have been observed, also cysts and teratomata. "Lime" and "sand" are sometimes found in the gland, just as in the choroid plexus, and while perhaps more likely to occur later in life, may be present at any age (Schüller, Vincent). Such deposits when very abundant can be identified in profile roentgen-ray film. The credit of first noting this interesting fact is due to Schüller.[1] The pineal shadow is to be looked for about 1 cm. behind and 4½ cm. above the external auditory meatus. Schüller notes that a normal-sized shadow is against the diagnosis of pineal tumor, and that a misplaced shadow may indicate pressure on the pineal by a tumor outside, or traction by a scar following healed syphilis or softening,

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[1] Deutsch. Ztschr. f. Nervenheilk., 1913–1914, **50**, 188.

Symptoms.—The symptoms of pineal tumor are those of new growth in the mesencephalon—cross-eye, choked disk, projectile vomiting, headache (chronic rather than paroxysmal) and fits. Before puberty there occurs at times also a phenomenal increase in growth, with sexual and mental precocity. Of this curious sign much has been said already (p. 309). In children it enables the clinical diagnosis to be sometimes successfully made. In adults the matter is much more obscure. A Wassermann test should, of course, be made, but even a 4+ reaction will not necessary prove the tumor to be specific.

Treatment.—The treatment of tumors is surgical. Operation is rather a forlorn hope, but is not always fatal. W. E. Dandy[1] has described an operation for pinealectomy, and has reported 3 cases. One patient (tubercle) survived eight months, and there were said to be no unfavorable mental or physical effects attributable to brain injury. Roentgen-ray exposures and decompressive trephining are also mentioned in the literature.[2]

Inflammations.—Inflammations need hardly detain us. Tuberculosis and lues may occur, but rarely except as parts of a generalized process. The same is true of the coccus inflammations and of epidemic encephalitis. Treatment is only of academic interest.

SECRETORY DISORDERS OF THE PINEAL GLAND.

If, as we have grounds for supposing, the pineal gland is a gland of internal secretion, that secretion may be, of course, as elsewhere, increased, diminished or absent.

The causes and symptomatology of the three possible conditions have been sufficiently treated in the previous sections.

Diagnosis and Treatment of Secretory Troubles.—From what has been already said, the principles of diagnosis and treatment may be readily inferred. Hyperpinealism will doubtless always be a surgical matter. Apinealism is not much more than a curiosity of medicine. Hypopinealism in varying grades is probably not so very uncommon among backward children. It is to be suspected in infants and young children (not Mongols and not cretins), where there is a small body and retarded intelligence. The 2 patients described (pp. 311 and 312) were possibly true cases of extreme hypopinealism. But many other less retarded children in my care have done well on pineal gland. It ought to be much more extensively employed than it is. Failure is often due to incomplete study of the case in hand, or to the use of an inert medicament.

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[1] Surg., Gynec. and Obst., 1921.

[2] Lereboullet: Prog. méd., 1922, p. 75.

As regards the first cause of failure, I am constantly urging it upon my students that mental backwardness in a child is a vague term covering a multitude of unknown conditions. Outside the cretins and Mongols but few generalizations are possible. Each case must be examined with systematic and conscientious care. The hair and bones must be considered. The spinal fluid must be examined. The teeth are of special importance. I am constantly surprised at the lack of interest which physicians take in the abnormal child's dentition. The time and place of appearance of the milk and permanent teeth, the size and shape of the teeth themselves, the enamel covering, the chalk lines, the spacing—all these points are of great value, and the progress of dentition during treatment is also of the first importance. Roentgen-ray films of the teeth and the skull are indispensable to the diagnosis, and well worth the extra time and money that must be spent on them. The interpretation of pineal shadows must be very conservative (p. 320).

When all this work has been carefully performed and verified, it will soon become evident to the candid observer that glandular deficiencies are often multiple. In these cases pineal gland must be combined with the additional gland or glands indicated, and in such doses and for such periods as each case requires. This does not mean giving indiscriminately to all patients the ambitious pluriglandular assortments gotten up by drug clerks in wholesale pharmaceutical establishments; but a rational adaptation and re-adaptation of each constituent to the condition of the patient at the time of observation.

As regards the second cause of failure, it is easily avoided if one will take the trouble to do so. There are now several New York dealers who specialize in standardized preparations of the glands of internal secretion; and if the attending physician hopes for results in any way satisfactory, he should hesitate at leaving this vital matter to the drug clerk to decide for him.

ADMINISTRATION OF PINEAL GLAND.

Dana and Berkeley[1] suggested a physiological method of standardizing pineal gland. This consists in checking the weight of the glands against the average weight of the calves or young bullocks it came from, and allowing one dose of gland for 150 pounds of live bullock. The method seems to work out pretty well at the bedside. This preparation may now be had in the market. It comes as tablet, capsule or hypodermic. It absorbs from the alimentary canal very well, and I have not heard of any irritation even from large overdoses. Usually three or four tablets a day are enough for the runabout child, and a proportionately smaller dose for sucklings, to whom it is best given suspended in milk. The best results are, of course, from dosage which best imitates Nature's method—small and frequent amounts continued through a long period, and by a long period I mean not days and weeks only, but months and years.

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[1] Loc. cit., p. 311.

When using unstandardized dried gland, $\frac{1}{10}$ to $\frac{1}{5}$ grain is a perfectly safe introductory dose. "Epiglandol" is a hypodermic preparation in clinical use in Germany.

One possible corollary to its successful effect in stimulating the sluggish mind of the backward child is the apparent quickening of senile mental processes which pineal gland sometimes produces. Within the obvious limitations it seems to be a valuable mental stimulant for old people, and is not followed by depression. I have had several elderly patients who positively declined to go without it after having given it a fair trial. But this question is one which is supported by purely clinical results, and is now only in the stage of hypothesis. There must be general clinical confirmation from widely different sources before it can be accepted by the "reasoned skeptic."

From pineal gland given orally to adults between the ages of twenty-five and fifty years (a large number of cases) I have never noticed any effect, either nervous or metabolic. C. von Noorden[1] found daily injections of "epiglandol" useful for increasing the weight of emaciated and undernourished patients (properly selected, of course) who were failing to assimilate an abundant balanced ration. In one very thin young married woman in my care, who for cosmetic reasons wanted to grow fatter, it turned out in six weeks that the "brilliant" results of pineal medication were probably due only to coincident conception.

There are a few additional scattered references to pineal medication in recent literature. R. Hofstatter[2] had good results in a few cases of nymphomania. O. Marburg[3] saw mental improvement in a backward boy who masturbated. To fit the case to his theory of the action of the gland, he explains that the mental improvement was secondary to relief of the sexual precocity indicated by the disposition to masturbate.

[1] Klin. Wchnschr., July 1, 1922.

[2] Monatsschr. f. Geb. u. Gynäk., 1917, **45**, 220.

[3] Loc. cit., p. 309.

CHAPTER XI.

THE THYMUS BODY.

This organ has been known time out of mind. The word is directly from the Greek, *θύμος, thyme,* and was applied by Galen to (1) warty growths (fancifully resembling a bunch of thyme), and (2) the thymus body. As *sweetbread* the thymus of calves and lambs is familiar in the meat markets.

The thymus has long been supposed to be a ductless gland, and is generally thus called to-day, but its physiology is imperfectly understood. Only an outline of the present status of the scientific problems involved can be attempted. On later pages especially interested readers will find fairly complete references to the literature.

ANATOMY OF THE THYMUS.

Gross Anatomy.—The thymus body in man lies in the front of the thorax, above the pericardium, anterior to the windpipe, behind the manubrium sterni; its upper border sometimes extends into the neck as high as the lower border of the thyroid. Its color is pinkish-white; its shape is irregular, generally bilobular; at puberty it averages 5 by 4 by 0.6 cm. in size. In the new-born, according to statistics of Bovaird and Nicoll,[1] it weighs on an average about 7.7 gm.; at puberty, 25 to 35 gm. Throughout adult life it gradually decreases in size and weight, though probably not so much as autopsies indicate, these being often done on persons dying of wasting disease.

Accessory Thymuses.—Accessory thymuses are sometimes present in man, very common in cattle, sheep and many other animals. The dog (Fig. 52) has but few, and the dog is in consequence apparently the safest animal to experiment on.

Microscopic Examination.—Microscopic examination (Fig. 53) shows a *cortex* and a *medulla.* The cortex is full of closely crowded small cells, having many properties of lymph cells. They are supported by a connective tissue network. The medulla has the same connective tissue, fewer lymphoid cells and a number of peculiar bodies called *concentric corpuscles of Hassall* (Fig. 54). These have a nucleus of one or more granular cells surrounded by imbricated "epithelioid" cells.

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[1] Arch. Pediat., 1906, **23**, 641.

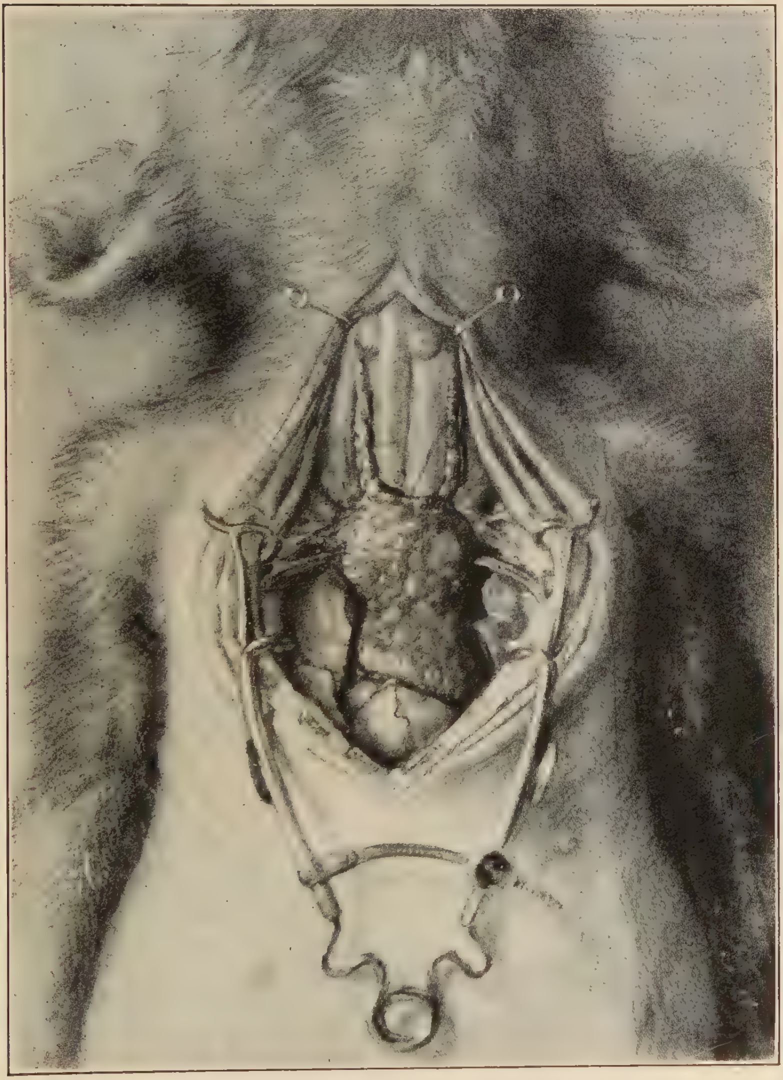

Fig. 52.—Dissection showing thymus of three weeks' old puppy. Cornua of thymus extend upward to thyroid, an arrangement less common in the dog than in the cat and some other animals. (Park and McClure.)

Comparative Anatomy.—The comparative anatomy is fully treated in the standard texts. Mammals and birds appear almost uniformly to possess a thymus.

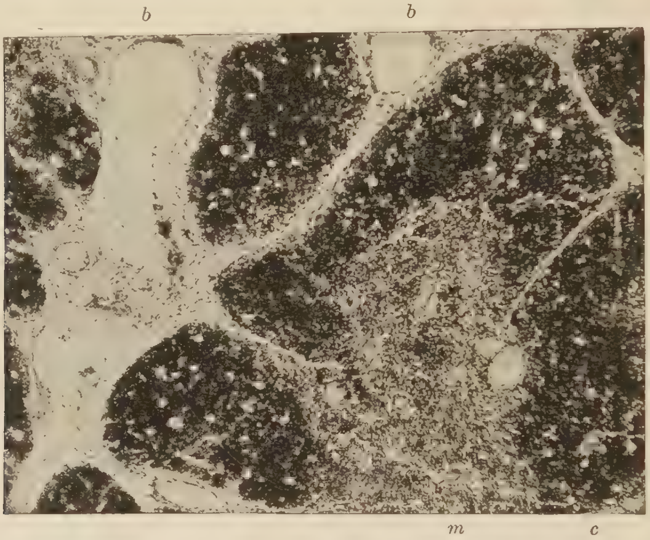

Fig. 53.—Section of part of lobule of thymus of child. × 60. *c*, cortex; *m*, medulla; *b,b*, bloodvessels in connective tissue trabeculæ. (Sharpey Schaefer.)

Embryology.—The embryology is disputed, the thymus seeming to be partly of entodermic and partly of ectodermic origin. For details the systematic works on embryology may be consulted.

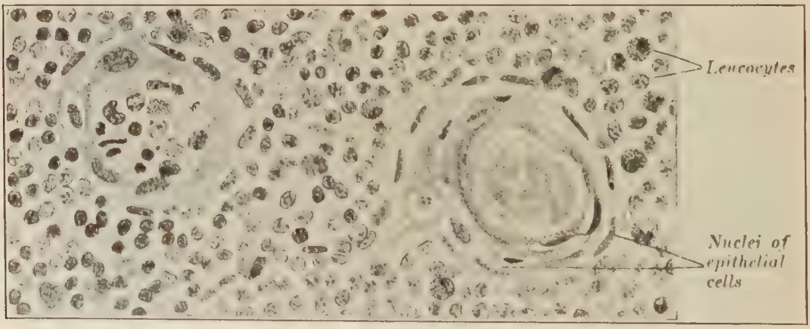

Fig. 54.—Section of Hassall's corpuscles; thymus of child aged six months. × 470. (Szymonowicz.)

S. Vincent's[1] account, while brief, is interesting, and I believe in accord with the most recent studies.

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[1] Loc. cit.

PHYSIOLOGY OF THE THYMUS.

Various Laboratory Observations.—The essential function, or functions, of the thymus are unkown. There is some ground for believing that it is related to the sex glands. Gellin[1] found that prepuberal castration in young rabbits was followed by puberal and postpuberal enlargement of the thymus, as compared with normal controls. Postpuberal castration was followed by a slighter but still quite evident enlargement. A general note on the nature and interpretation of such changes will be found in Chapter IX (p. 277). U. Soli[2] noted the same results after castration of cocks, guinea-pigs and rabbits.

Soli[3] has also noted some odd facts after thymectomy in hens. Four thymectomized hens (2 controls) laid eggs without shells for a period after operation. Several critical comments may be made. The subjects are few; the controls are insufficient; no data are given as to the supply of lime in the food. Another doubtful element is the lack of knowledge of accessory thymuses in hens; the operation may not have been a complete thymectomy. Poultrymen know that any hen will lay this kind of egg once in a great while, and they explain it as due to lack of lime in the food. But the phenomenon does not persist for weeks at a time, as in Soli's experiments.

Soli's work went unconfirmed for years, so far as I can find from the literature, until Oscar Riddle[4] found that in 5 pigeons, which were laying uniformly small or shell-less eggs, feeding dried thymus relieved the condition. In 1 other pigeon an imperfect thymectomy was followed by the laying of shell-less eggs, just as in the case of Soli's hens. Riddle concludes that in birds thymus secretes a true hormone, necessary to the production of egg-envelopes. His controls, made with various diets containing an excess of phosphate, vitamins and several ductless gland preparations other than thymus, were negative.

Uhlenhuth[5] reported that larvæ of certain species of salamander, fed on thymus, developed convulsions which could be relieved by parathyroid.

Experimental Thymectomy.—The complete history of experimental thymectomy to 1919, with copious references, is to be found in the exhaustive and interesting study by Park and McClure.[1] After a critical review of the multitudes of curious and contradictory findings previously announced, these authors give the full protocols of thymectomy in 75 suckling puppies. Twenty-one survived, and 19 controls were used. The technique of the operation was carefully worked out. Accessory thymuses were properly searched for at operation, and found absent at autopsy. The paper should be read in full by all special students. No abstract does it justice.

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[1] Ztschr. f. exper. Path. u. Therap., 1910–1911, **8**, 71.

[2] Arch. ital. de biol., 1909, **52**, 353.

[3] Pathologica, 1911, **3**, 118.

[4] Am. Jour. Physiol., 1924, **68**, 557.

[5] Endocrinology, 1919, **3**, 285, literature.

The authors conclude that the thymus in dogs is not essential to life, and that thymectomy produces no detectable alterations in either hair, teeth, metabolism, bones, muscles, strength, activity or intelligence of the subject animals. Moreover, it did not appear to influence growth, and it had no effect on ductless glands—or on *other* ductless glands, if thymus be one.

Autopsy Studies.—The morphological data of autopsy studies have been recently summarized in an important paper by J. A. Hammar,[2] who has made a specialty of thymus morphology for many years. This article should be read and re-read by all who wish to be fully informed of the vast labors expended on thymus pathology in the last twenty-five years.

Hammar's conclusions are partly as follows:

The thymus is an epithelial body infiltrated with lymphocytes. It grows until puberty, undergoes a relative involution after puberty, but retains throughout life—even in extreme old age—a certain size and a functioning cellular parenchyma. The old theory of an "age involution" of the thymus is certainly incorrect. With advancing years the connective tissue of the gland increases. This is accompanied in certain animals by the appearance of local areas of degeneration called "sequestral cysts." In human fetuses and small children affected with syphilis the same process appears prematurely ("Dubois's abscesses").

After death from disease the thymus is usually found reduced in size—accidental involution. Much more rarely there is a hyperplasia. Involution is also observed after starvation and wasting disease (a fact known for centuries), in pregnancy, and following roentgen-ray exposures. The involution of inanition is marked by increase of fat and disappearance of lymphocytes in the cortex, and later, in the medulla, by a relative increase but absolute decrease of the Hassall corpuscles. Even after extreme starvation this process may be reversed by feeding.

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[1] Am. Jour. Dis. Child., 1919, **18**, 317.

[2] Endocrinology, 1921, **5**, 543, 731.

The much rarer thymic hyperplasia has been noted in Graves's disease, Addison's disease, acromegaly, myasthenia and the so-called status thymico-lymphaticus.

Hammar further urges that a clear distinction must be made between "thymus asthma," caused by pressure of an enlarged gland on the trachea, and "thymus death." There is nothing to indicate that "thymus death" is due primarily to an abnormal condition of the thymus.

A further study of cases and literature prompts this author to the conclusion that the function of the thymus is antitoxic (see quotation from Barbàra, below). This, he states, however, confessedly only as a working hypothesis, and he urges further systematic research. A useful list of some 200 references is attached.

E. R. Hoskins[1] has reviewed the literature, and concluded that there is no satisfactory proof of a thymic hormone. The finding of Gudernatsch[2] that feeding of thymus to tadpoles delays metamorphosis has been thought by Uhlenhuth[3] and Hammar[4] to be due merely to a food deficiency. Uhlenhuth claimed that by adding other (non-glandular) items to the thymus diet he could produce metamorphosis at the normal time.

M. Barbàra[5] has assembled the literature and reported original studies supporting the view that the thymus assists in the formation of antitoxic bodies for the protection of the organism against infections, a view to which Hammar has been already quoted as inclining.

Metabolism During Thymus Feeding.—Halverson, Bergeim and Hawk[6] studied the metabolism of thymus (15 gr. daily of Armour's dried gland for five days) with a patient who had goitre. The diet was uniform for the period chosen, weighed and balanced. Results were not very conclusive. Thymus seemed to produce effects in some regards opposite to thyroid effects. There was particularly a diminished urine volume on constant intake of water. The authors give a useful list of metabolism references.

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[1] Endocrinology, 1918, **2**, 241.

[2] Am. Jour. Anat., 1914, **15**, 431.

[3] Endocrinology, 1919, **3**, 285.

[4] Loc. cit.

[5] Fisiopatologia della tiroide e del timo, etc., Milano, 1918.

[6] Arch. Int. Med., 1916, **18**, 800.

DISEASES OF THE THYMUS BODY.

INFLAMMATIONS OF THE THYMUS BODY.

Syphilis and tuberculosis of the thymus occur. "Dubois's abscesses" have been already mentioned on a previous page. Other inflammations are usually secondary to suppurative processes in the neck or anterior mediastinum.

TUMORS OF THE THYMUS BODY.

Benign and malignant thymomata are described. J. Ewing[1] thinks that many thymus tumors are, perhaps, manifestations of an infectious granuloma. Hyperplasias have been frequently described—some large enough to compress the trachea or bronchi, and cause severe inspiratory dyspnea. The treatment of this so-called "thymus asthma" is surgical. Death from asphyxia is not uncommon where the cause of the difficult breathing is not recognized in time.

STATUS LYMPHATICUS OR THYMICO-LYMPHATICUS.

This is a condition in which thymus and lymph nodes are enlarged, with certain general anatomical features believed to be characteristic. To surgeons the condition is of great moment by reason of the sudden death ("thymus death"), sometimes occurring when an anesthetic is administered to such patients. There is an immense literature. A good recent original study by D. Symmers[2] covers many of the details. W. Timme[3] believes that status thymico-lymphaticus is part of a pluriglandular syndrome. In the former of the references given this writer makes an admirable sketch of the anatomical appearances of status thymico-lymphaticus in its earlier stages.

PHARMACOLOGY AND THERAPEUTICS.

Chemical Studies.—Chemical studies of the composition of the gland show the usual organ proteids, nucleoproteids being of course very abundant. So far are we from understanding the function of the thymus that thus far there has been no question of isolating an "active principle," for no one knows what an active principle ought to do. Thymus extracts are said to lower blood-pressure, but this is a general property of organ extracts.

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[1] Neoplastic Diseases, 2d ed., Philadelphia, Saunders, 1922.

[2] Am. Jour. Med. Sci., 1918, **156**, 40.

[3] New York Med. Jour., July, 6, 1921; Endocrinology, 1918, vol. **2**.

Preparations.—The dried gland is to be had in the drug markets in tablets of 3 and 5 gr. The common commercial source is bullocks' or calves' thymus, from which the dealers remove the fat with a fat solvent, to prevent rancidity.

Clinical Uses.—In the present state of our knowledge it is rather idle to talk of "hypo-" and "hyperthymism." The clinical uses of thymus are entirely empirical.

P. Cohen has recommended thymus treatment for *arthritis deformans.* He reports an immense per cent of his patients cured or improved by this treatment. He recommends B. W. gland in doses of 30 and 40 gr. or more a day. In my hands the treatment has been disappointing, but the literature is not entirely unfavorable, and no bad effects have been noted.

By reason of the thymic enlargement in some cases of *Graves's disease,* thymectomy and roentgen-ray exposures of the thymus region have been recommended as a surgical treatment for this disease (Halsted[1]), with the customary stories of wonderful cures. I do not believe that this method of treatment is now practised anywhere by surgeons. Strange to say, there are also scattered notices in the literature of *thymus therapy for Graves's disease.* It may be at times a useful placebo when such is needed.

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[1] Loc. cit., p. 95.

CHAPTER XII.

INTESTINAL MUCOSA. MAMMARY GLANDS. SALIVARY GLANDS. SPLEEN. UTERUS. PROSTATE. CAROTID BODY. GLOMUS COCCYGEUM. PLACENTA. KIDNEYS.

INTESTINAL MUCOSA.

THE well-known work of Bayliss and Starling[1] indicated that acid chyme entering the duodenum starts the formation of an internal secretion or "chemical messenger" (hormone), which, though all the nerves to the pancreas be cut, nevertheless causes an active flow of pancreatic juice. To this substance they gave the name *secretin*. It could be got by boiling the triturated duodenal mucosa with diluted hydrochloric acid, and was found nowhere else in the body. It was rendered inert by stomach and intestinal juices. It was never isolated in pure form, but could be obtained from various animals. The same authors[2] affirmed that secretin comes by hydrolysis of a *prosecretin* present in the intestinal mucous membrane, and that it stimulates the secretion of bile and succus entericus as well as pancreatic juice.

Secretin has been marketed as a digestive adjuvant under various trade names. Carlson, Lebensohn and Pearlman[3] confirm the previous observations that gastric and intestinal juices destroy it. They conclude that it has no therapeutic value *per os*. I know of no therapeutic reports on hypodermic preparations.

A substance, *gastrin*, has been gotten from the gastric mucosa by a similar process. Luckhardt, Henn and Palmer[4] affirm that there is a lack of specificity in so-called gastrins and secretins, and Vincent, quoting from later authors, states that secretin is probably not a hormone, but an artefact which happens to have a secretagogue action. This also is disputed. For recent literature and data Cowgill and Deuel[5] may be consulted.

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[1] Jour. Physiol., 1902, **28**, 325.
[2] Ibid., 1903, **29**, 174.
[3] Jour. Am. Med. Assn., 1916, **66**, 178.
[4] Am. Jour. Physiol., 1921, **59**, 457.
[5] Ibid., 1924, **69**, 568.

FEMALE MAMMARY GLANDS.

The female mammary glands have been assigned various pleasing hormonic functions by popular medical writers. There is little or no concurring scientific or clinical evidence for such functions (p. 294). The glands are evidently *acted upon* by various hormones, but the modus operandi is very much disputed and is entirely in doubt. (For the action of liquor pituitarii on the mamma, see page 170.) There is a general clinical impression that the sensory stimulus of nursing on the nipples of the mother results in a series of contractions of the *post partum* uterus (often painful), and that involution is promoted thereby. The effect *may*, of course, be hormonic; it is generally thought to be a nervous reflex, comparable to the effect of food in the empty stomach on the peristalsis of the intestine.

Desiccated mammary gland has been given by gynecologists for uterine flooding and menorrhagia.

SALIVARY GLANDS.

The salivary glands as organs of internal secretion have been thought to be associated with carbohydrate metabolism. Their microscopic similarity to the pancreas perhaps suggested the relation. Experimental excisions with doubtful or negative results have been reported. There is quite a large literature.

THE SPLEEN.

The history of this organ and of the various ends it has been supposed to serve in the animal economy would fill a large book. The ancients made it the seat of the emotional quality still called by the same name. The English theologian, Paley,[1] bravely declared it a mere *stuffing* to hold the abdominal viscera in place. Later and more pretentious theories have imputed to it an immunity mechanism, a red-blood-cell-destroying function, a red-blood-cell-building function and of course an "internal secretion." The last view seems certainly to have been held by Claude Bernard.

Whatever the purpose of the spleen, splenectomy is in itself, though surgically a major operation, not fatal. Accessory spleens might in some of the cases prevent trouble, but in many of the successful splenectomies no accessory spleens were found. Its work seems either performable by other organs, or is in itself not essential to life. Modern references may be found in the new physiologies.

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[1] Natural Theology.

THE UTERUS AND PROSTATE GLAND.

In respect of the uterus and prostate gland there is no definite evidence of hormone formation. Marshall[1] gives recent references to the mostly controversial researches. G. Mendola[2] publishes with literature some recent fragmentary studies of the supposed endocrine relations of the prostate to surgical immunology.

THE CAROTID BODIES.

As to the carotid bodies, which are two minute masses of cells in the forks of the internal and external carotid arteries, there are a few contradictory studies. Betke[3] removed the carotid glands in dogs, and observed rachitis as a consequence. This might have been easily caused by bad food, insanitary surroundings, and malnutrition. Vincent states the carotid bodies to be merely bits of chromaffin tissue, and L. B. Arey[4] positively confirms the same view. From a recent laborious embryological study Christianna Smith[5] finds that the carotid body is a mixed structure, and that according to the species studied chromaffin cells may be many, few, or entirely absent.

THE GLOMUS COCCYGEUM OR COCCYGEAL BODY.

The glomus coccygeum or coccygeal body (*Steissdrüse* of Luschka, 1859) was supposed by that writer, with due reservations, to be a gland of internal secretion. Of later writers some have called it a chromaffin body, and some have identified it with the vascular system (an arterio-venous anastomosis). L. B. Arey[6] states that "Its affinities are obscure, but at no time does it resemble a chromaffin body."

THE PLACENTA.

About the placenta, as an endocrine organ, there has been abundant speculation, but the experimental literature is entirely unconvincing. The odd fact that many mammalian mothers (the cow, *e. g.*) *eat* the placenta has suggested that placental extract should be used as a remedy for subinvolution of the uterus, and as a stimulant for the mammary glands (galactagogue). Placental extract is actually sold by the dealers for the these purposes. Carefully observed results have been so far clinically doubtful, that is to say, negative. Even if successful, they could hardly be called anything but pharmacological.

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[1] Loc. cit., p. 282.

[2] La funzione endocrina della prostata e del testicolo, etc., Tipografia coöperativa, Roma, 1924.

[3] Beitr. z. klin. Chir., 1915, **95**, 313.

[4] Developmental Anatomy, Philadelphia, Saunders, 1924.

[5] Am. Jour. Anat., 1924–1925, **34**, 87, references.

[6] Loc. cit.

E. Hermann's claim of ten years ago that a growth-promoting lipoid can be extracted from placenta has been partially confirmed by Edgar Allen and coworkers,[1] but there is no proof as yet that this substance is a true hormone.

THE KIDNEYS.

Experimental physiology in the case of the kidneys has revealed many interesting and curious facts of late years. The new text-books of physiology may be consulted for details. None of the new work, however, gives any evidence that they have an internal secretion.

For chronic Bright's disease organotherapy with dried kidney substance is loudly advocated in certain commercial circulars. Scientific medical literature does not support the claim.

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[1] Loc. cit., p. 282, references.

CHAPTER XIII.

RELATIONS OF THE GLANDS OF INTERNAL SECRETION TO ONE ANOTHER.

This chapter may be some day one of great length, a large body of facts well-buttressed by scientific evidence and as fully accepted by the thoughtful physician as the theory of the circulation of the blood now is. But at present a grievous confusion reigns. Almost any layman—even newspaper editors and the directors of physical culture institutes—is at liberty nowadays to enlarge upon the "marvellous interrelations of the ductless glands" and the "domination of personality" by this and that combination of secretions.

To contradict *seriatim* the thousand fanciful and irresponsible assertions, medical and lay, on the subject would be an endless task. To quote references to entirely indecisive clinical and laboratory observations—half pointing one way and half another, and all disputed—is productive only of intellectual vertigo, and would serve no useful purpose, for by a logical process one cannot hope to rid men of conclusions and convictions not arrived at by logic. I shall content myself with a brief critical statement of the few generally accepted and scientifically proved facts; and I make no apology for not doing more.

Eppinger, Falta and Rudinger[1] have supposed with some show of probability that a disease of any single gland has two actions: (1) On the body tissues and (2) on other glands. How extensive these changes may be, however, is matter not for supposition, but for laboratory study and careful clinical observation.

Thyroid Gland.—If we accept as a satisfactory working hypothesis the claim of Kendall,[2] that this gland catalytically regulates the speed of chemical action in all parts of the animal economy—the formation of fat, the nutrition of muscle, the chemical changes of thought, the processes of digestion—we may then safely assume that it also modifies the nutritive processes of the cells in all the other glands of internal secretion.

When the thyroid is experimentally removed, accessory thyroids may act for it vicariously, and grow more cells. When this has happened (and it often does happen), elaborate reports on the condition of other glands—the literature is full of such reports—are entirely valueless. If there are no accessory thyroids, the somatic condition of hypothyroidism affects all other glands, and as myxedema approaches they doubtless do "enlarge," as the autopsy reports so often state; but as the other glands, so far as known, contain no iodine, (p. 170) it seems stultifying to call their enlargement "vicarious." It is much more probably a local manifestation of the general myxedema, and is accompanied by depression of function. We have thus in the cretin depression of the gonads, with sexual infantilism; depression of the pituitary, with failure of bodily growth; and presumably a depression of the other internal secretions, though of this one must speak with caution, for the clinical signs are much less dependable, and the chemistry is unknown.

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[1] Ztschr. f. klin. Med., 1908, **66**, **1**.

[2] Loc. cit., p. 48.

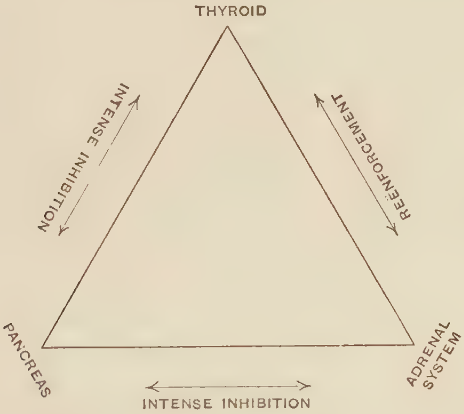

FIG. 55.—"Triangle" of Eppinger, Falta and Rudinger, showing supposed interrelations of thyroid, pancreas and adrenal.

Thyroid and Adrenals.—When the thyroid is enlarged, and simple hyperthyroidism is encountered, or when thyroid extract is given in large doses, we know that the heart beats faster, that the sympathetic outflow is stimulated in other ways, and that the blood sugar increases. As epinephrine also produces these effects, we may thence possibly conclude that the thyroid secretion has stimulated the adrenal medulla. But this is the old fallacy of "undistributed middle;" as glycosuria also results from stimulation of the pituitary (or injection of pituitrin), and from inactivation of the pancreas in other ways, a variety of other suppositions is possible. So far as I can learn, the famous "triangle" of Eppinger, Falta and Rudinger[1] rests on no surer foundation than this (Fig. 55).

[1] Loc. cit., p. 336.

A relation between the thyroid and the adrenal cortex is suggested by D. Marine.[1] He noted the benefit to patients with Graves's disease from treatment with adrenal cortex *given fresh.* This is an interesting observation, but it is isolated; it awaits confirmation.

Some experiments mentioned on page 222 indicate that the thyroid and the adrenals have something to do with the maintenance of bodily heat, but *just what,* is very obscure. Heat balance is a difficult subject. Even the pineal gland has been implicated in this process by Marburg (p. 309); for no better reason, so far as I can see, than that extracts of the pineal sometimes reduce blood-pressure, a property common to extracts of many organs in the body besides.

Thyroid and Pituitary.—These relations are mentioned in the paragraphs on the pituitary (p. 339).

Thyroid and Gonads.—The thyroid enlarges normally during menstruation in females. It also enlarges during pregnancy. The enlargement can be explained as a functional hypertrophy. The physiological conditions of menstruation and pregnancy make a greater demand upon the metabolism, and the thyroid is automatically stimulated to meet the demand. Nothing more than this is positively known. Those who have written enthusiastically about the elaborate interplay of the gonads and the thyroid, have of course, a personal right to their opinions, but the opinions ought to bear their true label—speculation. No *specific* chemical reactions are known.

The Parathyroids.—The relations of the parathyroids to other glands are very doubtful. Vines[2] has recently devoted a number of pages to the question, and after summarizing the claims of various authors, inclines to the view that parathyroid has no definite relation to other glands of internal secretion, except in so far as the supposed disordered metabolism of calcium modifies their vegetative cellular processes. An earlier and laborious review of the relations of the parathyroid to other glands is to be found in the paper by N. Guleke.[3] No important facts are proved.

C. E. Sajous[4] advocates the view that the "thyroparathyroid apparatus" is the chemical medium for the immunity reactions of the animal body against bacterial toxins. There is but little support for this position in current scientific literature. Both these glands participate essentially in the chemical processes of the body; but any specific relation they may bear to the immunity mechanism is unknown.

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[1] Loc. cit., p. 241. [2] Loc. cit., p. 128 (note.) [3] Loc. cit., p. 135.

[4] Internal Secretions and Principles of Medicine, 10th ed., Philadelphia, Davis, 1922.

The "thyroparathyroid antagonism" of some writers is mostly subjective. From the intimate anatomical relations of the two no conclusions can be drawn. Some cases of Graves's disease are reported to be benefited by giving parathyroid. But the "benefit" is only clinical evidence – the least reliable of all. When occurring (in my experience it has occurred rarely) it can just as well be explained as a symptomatic effect on the Graves tremor.

Pituitary Gland.—Our limited knowledge (as was supposed) of the functions of this gland has been rudely shaken by the studies of Bailey and Bremer. These studies, it is true, have not yet been accepted, but for the time they must be taken account of.

Supposing the experimental work of earlier writers to be ultimately confirmed, one may provisionally state that the stimulation of the gland (probably the posterior part) causes glycosuria and loss of fat, and hyperplasia of the anterior lobe speeds up growth in children, and increases the size of the entire skeleton in adults. Partial removal of both lobes is followed by increase of fat, arrest of growth (during the growing age), involution of the sex organs and sometimes polyuria.

This is a perplexing group of symptoms. It admits of no definite endocrine correlation except with the *sex hormones.* There seems no question that the pituitary has a specific connection with the gonads. The connection is somewhat supported by the pituitary swelling during oestrus and the cellular hypertrophy of the anterior lobe during pregnancy. This latter fact might find a simpler explanation in the demands the bony growth of the fetus makes on the mother, the fetal pituitary being only a secondary or intermediary agency. (Compare the thyroid enlargement in pregnancy.) The enlargement (questioned by some writers, p. 277) of the hypophysis following castration, and the increased growth of the bones following prepuberal castration might also be explained as a redistribution of growth energy not utilized in maintenance or development of the sex attributes. But the connection seems positively indicated by the gonad involution in later life incident upon the appearance of hypopituitarism. Until the pituitary and gonad hormones are isolated, the precise chemical reactions must remain a mystery. To speak of a "vicarious" enlargement of any gland for another of entirely different microscopic structure and physiological behavior is to give one's self over entirely to unscientific speculation.

Pituitary and Thyroid.—H. Cushing noted[1] "acute hypertrophy" of the thyroid after hypophysectomy. R. G. Hoskins[2] thought this observation quite enough to justify the presumption that thyroid and pituitary can act vicariously. Some carefully conducted experiments on tadpoles by E. R. Hoskins and M. M. Hoskins[1] were thought to point in the same direction. But I have just noted that to me this seems very improbable. The two glands differ remarkably in histology. Dried thyroid contains 0.2 to 0.3 per cent of iodine; pituitary, traces only. Some other explanation will probably be forthcoming when the experiments have been verified and repeated.

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[1] Jour. Am. Med. Assn., 1909, **53**, 249.

[2] Am. Jour. Med. Sci., 1911, **141**, 374, 535.

Increased adiposity follows both thyroid and pituitary deficiency, but it is also of ovarian origin, and the glandular interrelations, if any, are excessively vague. The metabolism of fat as a general subject is still one of great obscurity (see Chapter XV).

Pituitary glycosuria remains to be explained. Theoretically it could be a result of pituitary activation of the thyroid, or of the adrenal medulla. It could also be a direct depressive influence on the pancreas. But none of these suggestions has enough supporting experimental evidence in its favor to be more than a mere guess. Various small lesions at the base of the brain also produce glycosuria. The discussion by Macleod[2] gives some useful references.

Blair Bell[3] has a painstaking chapter on the gland relations of the pituitary.

To other glands than those mentioned the hypophysis has only hypothetical relations.

The Adrenals.—Upon review of the chapter on the adrenals the reader will be able to judge for himself how inadequate our knowledge is of the connections of this gland with others.

The *cortex* is a *terra incognita*. Hypernephromata (hyperplasias) arising from the cortex itself (not, it is said, from aberrant rests of cortex in other organs) are supposed when occurring in boys to hasten puberty, and in girls and women to further the production of feminine pseudohermaphroditism. Not all hypernephromata do this, but the cases, while rare, have been numerous enough to lend some probability to the hypothesis that an endocrine interrelation is involved. The exact chemistry of the details is entirely unknown. Krabbe[4] has tried to explain the phenomenon as due to embryonic inclusion in female adrenals of testis rests. The opposite condition (masculine pseudohermaphroditism) has been so rarely observed as to cast doubt upon its even occasional occurrence.

Cortical hypoadrenia in Addison's disease is accompanied by medullary hypoadrenia also, but there is no definite evidence that any other ductless gland is selectively affected either in the plus or minus direction during the course of this disease.

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[1] Loc. cit., page 170.

[2] Loc. cit., p. 246.

[3] Loc. cit., p. 160.

[4] Loc. cit., p. 289.

The use of cortex in Graves's disease is mentioned on page 241.

The *adrenal medulla*, with its chain of supposedly accessory chromaffin bodies, has been the gland of all others where riotous speculation has made merry. The doubts, difficulties and contradictions of its own physiology are not diminished when the question of its glandular interrelations arises.

The possible relations of the adrenal medulla to the thyroid and pancreas have been already touched on (p. 337). The hyperglycemia and glycosuria resulting from stimulation of the medulla, from injection of epinephrine and from actual contact of epinephrine solutions with the exposed pancreas of experimental animals, are effects primarily pharmacological. An animal seems to thrive indefinitely (p. 222) without epinephrine of discoverable amount in the circulation. Whether there be a normal antagonism, an automatic regulative reaction, between insulin and epinephrine or pituitrin is unproved. The solution of the question must rest upon further research, especially upon research by students who have not made up their minds beforehand what is to be the result of their laboratory activities. Whether epinephrine and pituitrin are normally synergic in their pressor effects is unknown.

Finally, as regards speculations relating to the "hypoadrenal constitution," or the "adrenal personality"—a personality in which the adrenals by some mysterious alternation and combination of hyposecretion and hypersecretion of both cortex and medulla, and by reactions of these secretions with other endocrines, modify for weal or woe the physical structure, mental status and moral destiny of certain unfortunate individuals—the time is, to say the least, not ripe for such pleasing generalizations. Incidentally it may be remarked that the same is true for the "pituito-centric," the "thymo-centric" and the "thyro-centric" people. They belong as yet only to fireside legend.

In this connection a quotation from G. N. Stewart[1] is apt: "Pendel[2] speaks of the hypoadrenal constitution as a clinical and pathological entity first studied in Italy (constitutional angihypotony of Ferranini). In reading this paper and many others by 'clinical endocrinologists,' especially the French and the Italians, the physiologist can scarcely escape the feeling that here he has broken through into an uncanny fourth dimension of medicine, where the familiar canons and methods of scientific criticism are become foolishness, where fact and hypothesis are habitually confounded, and 'nothing is but what is not.' "

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[1] Endocrinology, 1921, **5**, 283.

[2] Ibid., 1919, **3**, 329.

The Pancreas.—The insulin-forming function of the pancreas is doubtless related to other endocrines, but the connection is not clear. The question is touched on in the paragraphs on pituitary, thyroid and adrenal relations.

That Graves's disease is sometimes associated with glycosuria has been mentioned (p. 70), and the obscurity of the physiological relations noted. Thyroidectomy in human diabetics and in depancreatized dogs may diminish the glycosuria, but this observation is also perplexing. The induction of a hypothyroid condition may possibly depress the general metabolism without exercising any specific effect on the production of insulin. Further study of the matter is required.

Whether *secretin* stimulates the internal secretion of the pancreas as well as the external has been studied by experimenters. So far as I can learn no clear results have as yet been published, but Vincent states that secretin and epinephrine are antagonists.

As to relations of the pancreas with glands other than the ones mentioned there are no facts.

The Gonads.—The relations of these organs to the other glands have been mentioned already in other paragraphs. The possible nexus between the pineal gland and the gonads is touched on in the paragraph on Pineal Gland.

Thymus.—The glandular status of the thymus has not been established. Its possible relations to infections, metabolism and growth have been discussed (Chapter XI). Whether the thymus is related as cause or effect to status thymico-lymphaticus is unknown. The thymus is enlarged in many advanced cases of Graves's disease. The etiological relations, if any, are discussed on page 69. A pluriglandular relation of the thymus is described by W. Timme (p. 330).

Pineal Gland.—In Chapter X it has been set forth in detail that precocious puberty appears sometimes in children, mostly boys, who have tumors, mostly teratomata, of the pineal gland. The Vienna school affirm this to be due to hypopinealism. This lifts an inhibition from the pituitary, the pineal gland being assumed to possess such an inhibitory power in normal life.

The inhibition theory is a pure assumption; that teratomata of the pineal produce hypo- rather than hyperpinealism is a pure assumption. Dana and Berkeley have suggested that if the pineal gland has any secretion at all the hormone probably acts directly on the sex hormones, or on the somatic metabolism. The question is *sub judice.*

CHAPTER XIV.

CLINICAL FORMS OF PLURIGLANDULAR DISEASE. GLAND-GRAFTING.

PLURIGLANDULAR DISEASE.

Etiology and Classification.—From attentive reading of previous chapters it will be clear that glandular disorders may easily concur. Sometimes they are: (1) *Primary.* Primary pluriglandular conditions may develop (*a*) *independently of one another* from congenital defects, or from accidents, operations or disease. Sometimes one is (*b*) *consecutive to another,* and a secretory interrelation exists. As an example of the former class one may instance double tubercular testis in a man with diabetes mellitus, or Graves's disease developing in a woman who has had both ovaries removed for disease; as an example of the latter, Froelich's disease, which starting as a pituitary disorder secondarily causes the gonads to involve. The pluriglandular disease described by W. Timme (p. 330) may also be mentioned here. Cretinism and myxedema produce a damaging effect on all other glands, though I have expressed the opinion (p. 336) that this is perhaps a generic chemical rather than a specific endocrine influence.

Many pluriglandular disorders, again, may be conveniently classified as: (2) *Secondary.* In going the rounds of hospitals for the insane and institutions for the feeble-minded, one constantly sees epileptics, idiots, paralytics and insane persons of all ages who have signs of multiple endocrine troubles—enormous obesity, polyuria, hypothyroid dulness, sexual anomalies. I deprecate the too easy generalization that in such cases the endocrine troubles are the prime causes. With distinct organic disease of the brain the endocrine defect is evidently secondary, and it is very apt to be secondary in all; endocrine therapy is only palliative.

Also among *backward children* with no discoverable physical stigmata, though the diagnosis of the primary condition is often impossible, it is usual to find several of the hormones secondarily deficient. Even in Mongols a distinct clinical improvement follows the administration of thyroid, pineal, pituitary and the proper gonad. But

Mongolism does not improve beyond a certain point; the essential pathology is probably not glandular. The same thing seems to be true of many morons, though calling a child a "moron" is far from making a diagnosis of his disease.

Symptoms and Diagnosis.—The symptomatology is that of the component elements; nothing can be profitably added to the several accounts already given for each gland. The diagnosis, also, must be made from the symptom-complex. It will be sometimes as easy as the recognition of either component separately; sometimes so difficult that in many cases, with our present dim lights, the most careful and repeated study may fail to clear up the exact nature of the combination.

Prognosis.—No general statement can be made. The individual patients are all different. In primary defects, as we have described these, the prognosis is better; in secondary defects there is a wide range of results between absolute failure and relative improvement. In backward children (without organic marks) considerable improvement may be sometimes noted. The greater the defect, and the older the patient, the less the hope. Where epilepsy, brain tumors and incurable insanity have existed for years, coëxisting pluriglandular conditions are of small moment, as the general prognosis is hopeless.

Treatment.—The treatment of pluriglandular troubles is simply that of each disorder separately, as set forth in the previous chapters of this book. Hypersecretory disorders are to be met *secundum artem*. Hyposecretory troubles may be treated by any reasonable combination of gland extracts that the case calls for. Except for the pharmacological antagonism between insulin on the one hand and epinephrine and pituitrin on the other, there are few or no therapeutic incompatibilities between the various hormones that need give us pause at the bedside. Contraindications will be mostly those noted for each gland in previous pages. No one would be rash enough to give epinephrine for Graves's disease, or in patients with a blood-pressure of 200. But perhaps on the contrary adrenal cortex (p. 241) may be of value in Graves's disease. In all cases of depressed metabolism, of retarded metamorphosis (sex development), and of diminished growth movement, thyroid and anterior pituitary, probably also pineal, will act synergically. There do not appear to be any contraindications for gonad therapy in properly selected cases, unless one should mention here the experience of J. C. Hirst[1] in giving ovarian extract to pregnant women with goitre. The facts with regard to the influence of adrenal cortex on the development of the sex functions are too obscure to make therapeutical combinations of this gland with others more than pure guesswork.

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[1] Loc. cit., p. 303.

With backward children of the classes mentioned above the secretory trouble is usually a deficiency—and, as I think, a secondary deficiency—of several glands. The general principles that should govern one's clinical work in such problem cases have been already explained at length in the chapter on Pineal Gland. An effort must be made in a rough clinical way (smaller children can rarely be kept quiet enough for a basal metabolism test) to estimate the amount of each deficiency, and the dosage should be adjusted and readjusted for each patient. I deprecate very much the slovenly habit of giving indiscriminately the ready-made "shotgun preparations" of a half dozen different hormones for sale in the shops. The pharmacists could not sell these formulas if the physicians did not prescribe them.

Endocrine treatment of all "gland children" must be patient, and kept up in small doses for years. While cure is not to be hoped for very often, backward boys and girls frequently improve enough in the passage of time to become capable of doing some useful work.

In frank cretinism, also, it has seemed to me useful in practice to supplement the action of thyroid given in proper doses, with whole pituitary, pineal and the proper gonad. When the patient is carefully watched pluriglandular therapy can at least do no harm.

GLAND-GRAFTING.

The word *graft* (old English, *graff;* French, *greffe*) seems to derive finally from the Greek verb, *γράφειν*, write; the reference being apparently to the pen-like or feather-like semblance of twigs grafted upon fruit trees.

Grafting.—Grafting as an arboricultural device has been well known since history began. But while successfully done in trees and plants of the same species, grafting is much more limited in the animal kingdom, and among the mammals the process is hedged about with many difficulties. Failure can no longer be attributed to rude technique, and the supervention of bacterial processes. Later studies have indicated that specific differences in the chemistry of the tissues brought together are the prime obstacle to success. Up to the present no way has been found to avoid this obstacle. Skin-grafting from one part of a patient's body to another part of the same patient is frequently successful; transfer of skin from one patient to another is not always a failure. But the chemical differentiation of organs is much greater, and the nervous and vascular balance more easily disturbed. Transfers of bits of liver, pancreas, thyroid, or kidney from one part to another of the same man may succeed; bone-grafting from tibia to backbone of the same man may be done; but even in the hands of the most skillful technicians transfer of organs from one man to another is so rarely successful that doubt is cast even upon the few successes reported from time to time.

As has been incidentally explained elsewhere, grafts of organs and tissues may be made in several different ways, and some awkward words have been devised to describe the process:

(1) *Isoplasty,* or *autoplasty,* is a transfer from one to another region of the same individual; (2) *homoioplasty* is a transfer from one animal to another of the same species; (3) *heteroplasty* is a transfer from an animal of one species to an animal of another species.

The possibility of grafting is not to be decided *ex cathedra.* It is a question for experimental determination. But the great mass of experimental evidence up to the present time in man is against the clinical practicability of anything except isoplasty (A. Carrel[1]). A careful examination of the reported experiments of numerous observers seems to indicate that homoioplasty is more apt to succeed in the common laboratory animals than in man, and especially in the grafting of the gonads; but here also there are many failures, and many opportunities for deception of the experimenter.

The surgical details of gland-grafting need not be noted here. It goes without saying that asepsis must be perfect, that the graft must be fresh, warm, not too large and must be planted in a well-vascularized part of the new host's body. W. S. Halsted thought after many experiments with parathyroid that the condition of success was that the new host should be clinically in need of the the secretion of the gland to be grafted. Other writers, on the contrary, affirm that the graft grows better when the systemic demand upon its function is not too great. The two remarks indicate at least the extent of our ignorance. The surgeon should attempt an isoplasty at once if one or more of the parathyroids have been removed or their blood supply damaged in thyroidectomy (p. 135). Isoplasty is also indicated when double castration or double oöphorectomy is necessary, and a part of one or the other gland is capable of being separated in normal condition from the mass removed. Isotransplants of other organs are also theoretically possible. In dogs isotransplants of pancreas are placed under the skin with a drain to release the external secretion; otherwise cysts occur.

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[1] Loc. cit., p. 347.

A. Carrel[1] has described fully the technique, difficulties and limitations of organ transplantation, vessel and limb-grafting, and the effects of denervation on organs and tissues. More recent literature seems very generally to have confirmed his views.

Homoioplasty succeeds, as just noted, far less often than isoplasty. Reported successes have been largely based on the apparently successful functioning of the graft. But this seems to be mainly due to slow absorption by the host of the cellular contents of the graft. The graft itself generally becomes fibrous. A typical recent example of parathyroid homoioplasty is quoted on page 136. In man the psychic effect of the operation is also to be considered, when good results are reported.

It cannot be stated that success never occurs. The literature of the last twenty-five years contains occasional references by reputable surgeons of successful thyroid homoioplasty. R. T. Morris[2] reported that in a woman without ovaries in whom he grafted a fragment of an ovary from another woman, pregnancy and normal confinement about four years later occurred. The recent literature of testis homoioplasty is quoted on page 279. In laboratory animals homoioplasty of the gonads seems to have been successful in a few cases (p. 278). It is well known that many cellular tumors in mice and rats can be transferred to other individuals of the same species; but tumor tissue is perhaps less highly differentiated than gland tissue. Failure is, however, frequent, and in mankind failure of homoioplastic grafting is the rule (Blair Bell[3]).

As to heteroplasty, the general feeling among scientific men is that this is practically impossible. Occasional clinical successes (where the gland seems to grow, or at all events does not slough) are probably due to temporary cell absorption or to psychic suggestion.

S. Voronoff[4] reports many successes with monkey glands grafted into the scrotum of men. The candid reader of Professor Voronoff's accounts will admit that his work has been painstaking and sincere.

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[1] Bull. Johns Hopkins Hosp., January, 1907; Arch. f. klin. Chir., 1909, vol. **88**, with numerous references.

[2] Med. Record, 1906, **69**, 697.

[3] Loc. cit.

[4] Greffes testiculaires, Paris, 1923; Quarante-trois greffes du singe à l'homme, Paris, 1924, and later publications.

He has probably deprecated as much as anyone else the undesirable and premature notoriety which newspapers and the theatre have given the "rejuvenation graft." He admits that the operation sometimes fails, but thinks that improvement of technique and the selection of a more fortunate site may raise the percentage of successes. His experience indicates that Cynocephalus (baboon) is not so good a gland source as the chimpanzee, and he suggests very fairly that in view of the close zoölogical relationship between man and the primates, the graft cannot be strictly called heteroplastic.

My surgical friends in New York tell me that the operation has not met with any great favor in the United States. Undoubtedly a large number of unsuccessful cases have not been reported. Thorek[1] describes a new method of transplantation, and gives drawings of sections of monkey glands, vascularized and well staining, some months after having been grafted in man.

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[1] Endocrinology, 1922, **6**, 771; Wien. med. Wchnschr., 1923, No. 50.

CHAPTER XV.

ENDOCRINE INFLUENCES IN GROWTH, IN OLD AGE AND IN OBESITY.

PHYSIOLOGY OF GROWTH AND DEVELOPMENT.

THE physiology of growth and development both in animals and plants is a major biological problem and one of great complexity.

Plants.—In plants the size of the seed indicates only the amount of required growth before root and leaves can begin to assimilate from air and soil. In many annuals the limits of growth seem to be a unit character or factor in the chromosomes of the germ cells. However abundant the accessories of sunshine, soil-food and moisture may be, the pea (Mendel's original experimental plant), wheat-stalk or maize attains only a certain maximum height, then flowers, goes to seed and dies. But the climbing and running annuals, such as morning glory, nasturtium, pumpkin, bean, grow rather freely, and in the temperate zones nothing seems to stop them except frost and disease. Some garden plants originally tall or indefinitely climbing have been modified by selection, and become "dwarf" plants. Examples (nasturtium, pea, lima bean) are commonplace with gardeners everywhere. Whether endocrine influences are intermediary in these phenomena is very doubtful (p. 23).

Animals.—In animals the causes of growth and limits of size are not less obscure.

Insects.—In insects with a complete metamorphosis, like the mosquito, the larva grows rapidly, sloughing its case from time to time and attaining nearly the size of the adult before pupation. The imago emerges full-grown from the pupa case, and as soon as its wings are dry it eats, flies and couples, with but little subsequent addition to its size.

Vertebrates.—In vertebrates growth seems primarily to depend on increments in the size and length of the skeleton, which at first is made up of membranes (flat bones), and cartilage (long bones). Numerous *osseous centers*, both intermediate and peripheral, appear and enlarge in appropriate directions in the various bones of the skeleton, and when these centers finally coalesce growth is completed.

Mammals.—In most mammals, including man, there are well-defined limits of growth and of adult size. The endocrines participate in this process, but whether they are the only or the major determinants is unknown. It is a remarkable fact that the limits of growth in the European white man are so well regulated that 99 per cent of the adult population have a height of not more than 6 feet 4 inches, and not less than 5 feet. The vast majority of normal male adults have a weight of not less than 100 nor more than 200 pounds. Among the varieties or subvarieties of Homo sapiens there are racial strains which are short and fat (Hebrew), or short and well-proportioned (Japanese), or pygmies (certain African tribes). Selection has made differences of size still more striking in the various breeds of dogs. Possibly in mammals the factor for height resides in the chromosomes, as it does in the pea. But how the mechanism of growth is chemically intermediated, and how large a part is played by the endocrines, is unknown.

All breeders and veterinarians know that in large litters of pigs and puppies there is apt to be one "runt" or dwarf, which, while active and voracious, fails to grow. Explanation possibly lies in some peculiar imbalance of the hormones, but I know of no scientific studies on the subject.

Certain facts of clinical and laboratory observation throw some helpful light on growth. In the chapter on the Pituitary Gland it has been noted that human giants and dwarfs (the latter of certain kinds only) often have signs of pituitary dyscrasia. The bulk of the evidence points to the probability that hyperpituitarism in the growing years has a selective chemical influence on the osseous centers, increasing their growth, while it delays their coalescence. This produces overgrowth of the skeleton, with gigantism. Hypopituitarism seems to have the opposite effect and infantilism results. The growth hormone may be primarily modified in the hypophysis itself, or secondarily depressed by hypothyroidism.

There is overwhelming experimental and clinical proof that prepuberal castration increases the growth stimulus, producing taller and stouter men and women, and larger and heavier animals. This is possibly due only to a redistribution of the total growth energy (p. 277). It has been also supposed that the sex hormone exercises an "inhibition" upon the pituitary, and that this inhibition is lifted by castration. If this be true the precise chemical reactions are entirely unknown. In boys and girls early appearance of puberty is observed to be inversely related to the attainment of great height, but exceptions occur.

The weight and height statistics for boys and girls of various ages in institutions are much below the figures for children who are well fed and tenderly cared for in the homes of the well-to-do. This illustrates in the animal what rain, sunshine and a fertile soil do for the plant. But these influences are evidently secondary. Children put on weight in fall and winter, and grow taller in spring and summer. The endocrine relations of these facts are speculative. Recent statistical studies indicate that girls commonly cease growing at seventeen years, and boys at twenty and twenty-one years. The immediate anatomical event is doubtless the coalescence of the osseous centers in the spine and in the epiphyses and

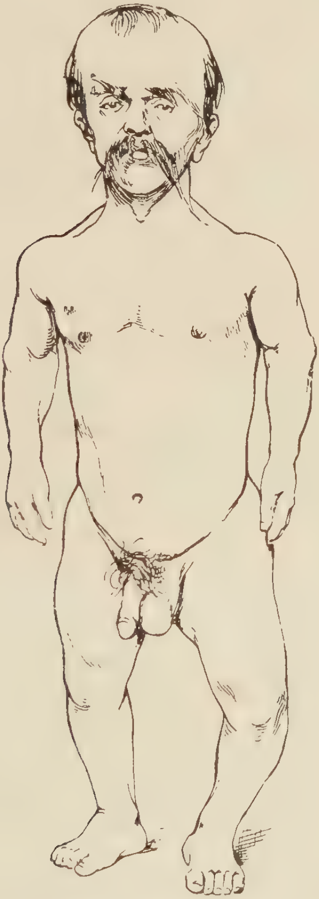

Fig. 56.—Chondrodystrophic dwarf. (Marie.)

diaphyses of the long bones. Except in so far as the facts of castration give a clue, one must again note that the endocrine factors in this coalescence are extremely obscure. The adrenal cortex possibly participates in the process, either independently or by way of the gonads.

The occasional occurrence of a normal trunk and long arms and legs, or long hands and feet (*arachnodactyly*), or of a good-sized trunk and short extremities (*acondroplasia*, *chondrodystrophy*) has been noted. The hormone relations, if such exist, are entirely unknown. The achondroplastic dwarf (Fig. 56), who has excellent brains in many instances, a good-sized head and trunk, well-developed sex organs, and infantile arms and legs, is a pathological puzzle which no one has so far explained. Thyroid medication is entirely valueless.[1] Recent interesting studies of arachnodactyly, with literature, may be found in the paper by Ormond and Williams.[2]

The influence of thyroid, pituitary and thymus on the *growth and metamorphosis of frog larvæ* has been discussed in various previous chapters.

The *growth energy of cellular tumors* is a difficult and obscure question. Thyroid, thymus and pancreas have been said to reduce the rate of tumor growth. The evidence is entirely equivocal. The occasional regression of breast cancers in women after double excision of the ovaries has been mentioned (p. 285).

OLD AGE AND THE ENDOCRINES.

Speculation on the causes of old age, normal, deferred and premature, has long been rife. The moralist enlarges upon virtue as the key to the lock. "Length of days and long life and peace" shall be added to the other rewards of righteousness. But there are, alas, many exceptions to this rule. By comparison of the growth period with the average length of life, man falls far behind the domestic animals. A horse is physically and sexually mature at two years; a cow, a dog, a cat, at one. The horse lives to be twenty and twenty-four years old, the cow to twelve or fifteen and the dog to ten or twelve. The whole life period of these domestic animals is therefore ten or eleven times the growth time; the life period of man is on the average only two, and at best only three or four. With man unfavorable hygienic conditions, the struggle for existence, the relatively greater incidence of acute disease, the special causes of arteriosclerosis, all contribute to premature death and senile decay. Whether there is any *primary* influence to be traced to the endocrines is speculative. Replacement of the sex organs, even if perfectly successful, is far from causing a rejuvenation of the entire body. Gray hair, calcified cartilages, thickened arteries, high blood-pressure, stiff joints, relaxed muscles and decay of mental initiative—these make a symptom-complex which defies endocrine analysis. Old age and death are normal biological events—*lex, non pœna, mors.* The ductless glands themselves grow old. At present there is no scientific knowledge that *explains* normal old age. It is one of the ultimate facts of biology.

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[1] Holt and Howland: Diseases of Infancy and Childhood, 8th edition, New York, Appleton, 1923.

[2] Guy's Hosp. Repts., 1924, **74**, 385.

In respect of premature old age (*senilism*) there are some endocrine factors. Rapid senescence has been described as a marked sign of Simmonds' disease (p. 202). Signs of old age multiply with increased speed after the normal climacteric in men and women. Baldness and gray hairs have been attributed—often without any reasonable ground—to various endocrine disorders. High blood-pressure and atheroma of the arteries have been observed in concurrence with primary tumors of the adrenal medulla, but a causal nexus is not established. Arteriosclerosis also follows often enough on double excision of the sex glands to justify some suspicion that the relation is one of causation. Of course, chronic hyperthyroidism presently breaks down the heart and raises the blood-pressure.

On the whole, however, one is rather forced to conclude that premature old age is in the main caused by misuse and abuse of the human machine, by industrial poisonings (especially lead) and bacterial invasions (especially syphilis). The endocrine glands seem to play only a secondary part.

Among the curiosities of medicine must be mentioned the 3 cases of *old age in children* described by Hastings Gilford.[1] Gilford called the condition *progeria,* and considered it a mixed infantilism and senilism. An autopsy on one of the patients, dying at the age of eighteen years, was indecisive as far as the state of the ductless glands was concerned. Various endocrine explanations have been offered. All are entirely speculative. In one case, a boy, aged seventeen years, Gilford called attention to the "Skinny, beaked nose, revealing the outlines of cartilages, the thin lips, the ill-developed lower jaw and clavicles, wasted ear lobules and the scanty gray-white hair; also the extreme leanness, the poor musculor development, the large knuckles of the hands, the absence of sexual hair and the backward sexual development. Voice was piping. Many milk teeth were still in the jaws. Anterior fontanelle not closed. Intelligence was good. The boy stooped, walked with a stick. Disorder began in infancy."

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[1] Disorders of Postnatal Growth and Development, London, Adlard, 1911.

OBESITY AND THE ENDOCRINES.

The known anatomical and physiological facts relating to the distribution and metabolism of fat in the normal human body are easily accessible in the new text-books. Grafe's[1] account is encyclopedic.

Woman has more fat than man. It is abundant under the skin everywhere, and particularly abundant in the breasts, hips and thighs. This sex distribution first becomes marked as puberty approaches.

In both sexes fat is increased physiologically by reduction of physical exercise, by drinking alcoholic and malt liquors, and by an amount of food in excess of the caloric requirements for age, sex and occupation. Emaciation results from overwork, loss of sleep, mental anxiety, starvation and wasting disease.

Obesity is a degree of fatness not usually reached by physiological processes; but the stoutness of the habitual *von vivant* passes over by imperceptible degrees into obesity. Some writers call obesity *endogenous*, and ordinary physiological overweight *exogenous* adiposity. Obesity is more common in women than in men. The fact seems partly referable to their respective modes of life and dietetic habits, and partly to endocrine differences.

Non-endocrine Obesity.—There are many non-endocrine causes for obesity. Local *lipomatosis* may be a form of tumor. Racial obesity is also to be noted. The *adiposis dolorosa* of F. X. Dercum[2] has been much discussed. Two of Dercum's first cases had hard and partly calcified thyroids; but the endocrine relations of this disease are very vague. I. P. Lyon[3] has collected over 200 references, and reaches no very definite conclusion save that the disease is probably not a clinical entity.

Many patients with chronic emphysema are enormously fat. The trouble in this instance is generally supposed to be defective oxidation.

Endocrine Obesity. Causes.—Endocrine obesity arises from defective secretion of the *thyroid* and *pituitary*, and from various reactions of the *gonads*. The causes of thyroid and pituitary obesity have been sufficiently dealt with. Gonad obesity requires some further discussion.

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[1] Ergebn. d. Physiol., 1923, **21**, Part II, 197, 282, references.

[2] Am. Jour. Med. Sci., 1892, **104**, 521.

[3] Arch. Int. Med., 1910, **6**, 28.

Gonad Obesity.—This arises in various ways. Castration is a cause in either sex. Atrophy of the testes may be the trouble. In young women "dysovarism," with amenorrhea, sterility and anaphrodisia, is apt to be accompanied by obesity. Medical writers for centuries have commented on the fact. In men and women *after the climacteric* the causes of obesity are often obscure, and by no means always associated with gonad insufficiency, or with endocrine deficiency of any kind. Each case requires study. At this time of life the gonad is probably more often at fault with women than with men, and in practice ovarian therapy with women is much more often successful than testis therapy with men.

The rapid *gain in weight* of many healthy young men and women *immediately after marriage* is usually considered endocrine in origin. It is possibly plus-gonad, but it may also be attributable to the good digestion and assimilation that are naturally associated with the happiness of early married life.

Maternal obesity is supposed to be largely due to endocrine reactions, also possibly plus-gonad. It is often quite astonishing. A slender young woman of 90 or 100 pounds frequently after a first confinement puts on 50 or 75 pounds more, mostly fat. An interesting study of genital obesity in females, with literature, has been made by Berkowitch.[1]

Obesity and Diabetes.—In the text-books for many years obesity has been mentioned as one of the "predisposing causes" of diabetes. In the light of modern research overfatness might be better called the *first* effect, and diabetes the *second*, of overeating, especially of carbohydrate excesses—candy, cakes, sweet desserts and the *solatium magnum* of American youth, ice-cream soda.

Symptoms and Diagnosis.—For the symptoms and diagnosis of endocrine obesity previous chapters give sufficient details. It may be repeated here that thyroid obesity should not be diagnosed without a basal metabolism determination. If the basal metabolism rate is down to −20 or more, and there are clinical signs of thyroid deficiency besides, thyroid medication cannot do any harm.

Management and Medication.—Indications and contraindications follow from previous paragraphs. As to the administration of the respective hormones involved, full details have been given, and the indications for hypodermic use of pituitary and ovarian extract, and intravenous use of thyroid and ovarian extract, duly set forth.

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[1] Thèse de Paris, 1908.

There is no objection to giving thyroid and pituitary together if the symptoms point in the direction of combined deficiency. It may be even well to give thyroid, pituitary and ovarian (or testis) extract in one pill, except in the cases where thyroid has to be pushed; then it must be given by hypodermic, or in a separate tablet, though if desired still in clinical conjunction with the other hormones mentioned.

If there are no complicating general diseases the patient's diet should be balanced (p. 260), and the calories calculated for age, sex, weight and physical activity. A diet list should be written for each individual patient, and information provided as to the calorie values of ordinary foods. All food should be weighed. There is no special magic in gram weights; an ounce for feeding purposes is fairly equivalent to 30 gm., and unlearned patients are discouraged at the start by too much unfamiliar scientific "jargon."

The supply of food should be slowly diminished, and the medication slowly increased until the patient begins to lose about 1.5 or 2 per cent of his weight per month. To efface wrinkles in the face and folds of skin in the neck massage may be employed. Plenty of water should be drunk. Exercise should be adjusted to the needs of the individual case. Growing children must be measured as well as weighed; increase in height may mask a satisfactory relative loss of weight, unless one remembers this.

Results are often very satisfactory when the patients coöperate. Ordinarily they do the things that they find it agreeable to do, and neglect the others. But this very human failing must be patiently dealt with; perseverance accomplishes wonders. When absolute failure finally occurs, either the patient has persistently broken diet, or the medicine was inert, or the dosage was insufficient, or the diagnosis mistaken.

Under Froelich's Disease and Diabetes other useful general details as to diet may be found.

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